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Within-host mathematical modeling of antibiotic-phage treatments on lysogenic and non-lysogenic bacteria dynamics

Hyacinthe M. Ndongmo Teytsa^a, Ousmane Seydi^b, Berge Tsanou^{c,d}, Ramsès Djidjou-Demasse^{a,b,*}

^aMIVEGEC, Univ. Montpellier, CNRS, IRD, Montpellier, France.

^bCRISIN'2D, École Polytechnique de Thiès, Thiès, Sénégal.

^cDepartment of Mathematics and Computer Science, University of Dschang, Cameroon.

^dDepartment of Mathematics and Applied Mathematics, University of Pretoria, South Africa.

*Corresponding author: ramses.djidjoudemasse@ird.fr

Abstract

Bacteriophages, or phages (viruses of bacteria), play significant roles in shaping the diversity of bacterial communities within the human gut. A phage-infected bacterial cell can either immediately undergo lysis (virulent/lytic infection) or enter a stable state within the host as a prophage (lysogeny) until a trigger event, called prophage induction, initiates the lysis process. We develop an approach based on a model structured in terms of time since bacterial infection. We derive important threshold parameters for the asymptotic dynamics of the system and demonstrate that the model's qualitative behavior can range from the extinction of all bacterial strains to the persistence of a single strain (either lysogen or non-lysogen bacteria) or the coexistence of all strains at a positive steady state. We highlight the existence of critical induction rate values that lead to the coexistence of all states through periodic oscillations. We also conduct a global sensitivity analysis for an effective bacterial clearance. In scenarios where antibiotics are not sufficiently effective, we identify four key phage parameter traits: (i) the phage induction probability, describing the capacity of prophages to be induced, (ii) the probability of absorption, describing the phages' ability to invade susceptible bacteria, (iii) the reproduction number of susceptible bacteria in the absence of antibiotics, and (iv) the latent period, describing the time since absorption. The obtained results emphasize the effective therapeutic potential of selected phages.

Keywords: Within-host age structured model; Nonlinear dynamical systems; Antibiotic-phage combination treatments; Bifurcation analysis.

1 Introduction

Antimicrobial resistance (AMR) is a worldwide major crisis [1]. The lack of effective treatments to control pathogenic vibrios resistant to antibiotics has led to the exploration of new alternatives. One of the most promising options is the antibiotic-phage combination treatment. Indeed, including antibiotics in experimental phage treatments could be relevant for reasons of expediting regulatory approval for phage therapy and phages have been used in combination with antibiotics in various published clinical case studies [4, 32, 37]. Phage infections can lead to lysis and death of the infected bacteria, and new infections by progeny virus particles can drive down bacterial populations leading to endogenous oscillations in population densities [21]. However, for many bacteriophages, lysis is not the only possible infection outcome, because beside lytic phages, there is another type refer to as temperate phages. Infection by temperate bacteriophages such as phage λ , μ , and P22 can lead to cell lysis or lysogeny. Lysogenic conversion refers to the integration of a temperate phage into the bacterial genome and forms a prophage. As a genetic material, prophage might constitute up to 20% of the bacterial genome, with variation between species and strains. These prophages propagate vertically together with bacterial cell division

and induce spontaneously to enter the lytic cycle to form new bacteriophage particles either spontaneously or under the influence of various inducers. These new phages can then lyse or lysogenize other susceptible non-lysogens, thereby restarting the process and impacting the competition between lysogens and non-lysogens [5].

Small intestines are highly polluted by phages. One estimates that 10¹⁵ phages reside in the human gut, which accounts for approximately 10⁸-10¹⁰ phages per gram of human stool depending on the extraction method used [8, 23]. In the human gut, phages are capable to eradicate bacterial populations by lysis (virulent infection), but can also carry out horizontal gene transfer (HGT) through prophage integration (lysogenic infection). The acquisition of new genes provided by prophage can be favourable to the bacterial host with benefits including improved colonization of the gut, virulence factors, improved stress tolerance, biofilm formation, motility, or immunity in the case of prophages [10, 13]. Whenever gut commensals acquire genes conducive to virulence, they can evolve to become pathogens, thus, phages can contribute to the spread of virulence and disease development in the human gut. Indeed, prophages or phage genes have been detected in many pathogens. A classic example of this is some nonpathogenic *E. coli* strains residing in the human gut, but, which through the acquisition of phage-encoded Shiga toxins, can evolve into pathogens [13, 15, 25, 27]. These complex relationships between phages and their bacterial hosts in the human gut urge us to investigate the following research questions: (i) What could be the impact of lysogeny on the success of antibiotic-phage synergy therapy? (ii) If antibiotics are ineffective, what could be the most influential phage quantitative traits parameters to eradicate the infection ?

Several models have been developed to study the dynamic of phages and bacteria in the presence of the antibiotic and phage therapies (eg., [12, 19, 28]). In [28] authors developed a nonlinear population dynamics model of combination therapy that accounts for the system-level interactions between bacteria, phage, and antibiotics for in vivo application given an immune response against bacteria. In [19], authors derived a phage-antibiotic model to study the competition synergy between temperate and chronic phages. We extend previous works by explicitly tracking the "age" of the infected cell to accurately account for the delayed lysis and burst phenomenon of infected bacteria. The model proposed here includes two types of bacterial strains: susceptible bacteria (non-lysogens), which are not infected by a phage, and lysogens, which are infected by a temperate phage and transmit the prophage to their offspring through vertical transmission. Furthermore, an in-depth asymptotic analysis of the model's steady states has been conducted based on several threshold parameters, including the reproduction number of susceptible bacteria (\mathcal{T}_S), the reproduction number of lysogen bacteria (\mathcal{T}_L), the reproduction number of phages within an entirely susceptible bacterial population (\mathcal{R}_0^S), and the reproduction number of phages within an entirely lysogen bacterial population (\mathcal{R}_0^L). Through a precise analysis, we additionally highlight the existence of a Hopf bifurcation, which gives rise to periodic solutions around the positive steady state (ie., with the persistence of both bacterial strains). A global sensitivity analysis has been conducted to identify the most influential phage and antibiotic quantitative traits for effective bacterial clearance.

The manuscript is organized as follows. The model description as well as parameters are presented in Section 2. In Section 3, we introduce the main results of the manuscript. These include the existence of a globally defined semiflow of the proposed model, the asymptotic stability of the model's stationary states, an analysis of the Hopf bifurcation around the positive stationary state, and the sensitivity analysis results. Those results are then discussed in Section 4. Finally, Section 5 is devoted to the detailed proof of the main results of the manuscript.

2 The mathematical model

We derive in this work a dynamical model of pathogen bacteria within the host taking into account the ingestion of both phages and antibiotics for therapeutic purposes. The basic model of phages and bacteria has been studied in several studies (eg., [5, 11, 26, 27, 31]) without considering the effect of external interventions. Additionally, we assume that the antibiotic dynamics occur rapidly and reach a steady-state concentration denoted by \mathcal{C} .

At all time t , $P(t)$ is the density of phages within the body. During the antibiotic-phage therapy, bacterial population splits into three classes, namely: Susceptible/non-lysogen bacteria ($S(t)$), lysogen bacteria ($L(t)$) and lytic fated infected bacteria ($I(t, \cdot)$). Additionally, we track the time since phage absorption using the continuous variable τ , such that $I(t, \tau)$ represents the population size of lytically infected bacteria, which have been infected by phages since time τ . Therefore, at any time t , the quantity $\int_0^\infty \theta \mu(\tau) I(t, \tau) d\tau$ represents the total number of phages produced in lytic-fated cycle, where θ denotes the average number of phages produced after the burst and $\mu(\tau)$ represents the mortality rate of infected bacteria τ -time post infection. In our modeling framework, the action of antibiotics occurs at the level of bacterial replication (growth of bacteria). We then set by, $r(\mathcal{C})$ the growth rates of susceptible bacteria and lysogen bacteria, such that $r(0) > 0$, and as the antibiotic concentration increases, the reproduction rate approaches 0. Consequently, the antibiotic's effect is bacteriostatic. Similarly, susceptible, lysogen and lytic fated bacteria are eliminate by immune system at the rate ν . Susceptible bacteria are infected by phages at rate β (absorption rate). A proportion (π) of absorbed bacteria moves to the lytic-fated bacteria class, while the remainder $(1 - \pi)$ moves to the lysogens class. We denote α as the rate at which lysogen bacteria are induced into lytic fated bacteria. Overall, phages are characterized by several quantitative traits introduced above through parameters β , α , θ , and μ . We then denote the phage quantitative traits parameters by $\mathcal{P} = (\beta, \alpha, \theta, \mu)$. Finally, we schematically illustrate the phage-bacteria interactions in Figure 1. The model within the human host reads as :

$$\begin{cases} \dot{S}(t) = r(\mathcal{C})S(t)\mathcal{W}(S(t) + L(t)) - \beta S(t)P(t) - \nu S(t), \\ \dot{L}(t) = r(\mathcal{C})L(t)\mathcal{W}(S(t) + L(t)) + (1 - \pi)\beta S(t)P(t) - (\nu + \alpha)L(t), \\ (\partial_\tau + \partial_t)I(t, \tau) = -(\nu + \mu(\tau))I(t, \tau), \\ I(t, 0) = \pi\beta S(t)P(t) + \alpha L(t), \\ \dot{P}(t) = \int_0^\infty \theta \mu(\tau) I(t, \tau) d\tau - \beta S(t)P(t) - \delta P(t). \end{cases} \quad (2.1)$$

The function \mathcal{W} accounts for the regulation factor of the bacteria growth. We assume that \mathcal{W} is continuous and decreasing. We assume that \mathcal{W} is continuous, decreasing and there exists w_0 (either a positive constant or $+\infty$) such that

$$\mathcal{W}([0, w_0)) = (0, 1]. \quad (2.2)$$

Such a function encompasses the classical logistic growth,

$$\mathcal{W}(x) = 1 - \kappa x, \quad (2.3)$$

or functions of the form

$$\mathcal{W}(x) = (1 + x)^{-\kappa}, \quad (2.4)$$

with κ a positive constant.

3 Main results

3.1 Preliminary remarks and assumptions

This section is devoted to some preliminaries including the abstract formulation of Model (2.1). We will make use of the following quite general assumption.

Assumption 3.1 *The function \mathcal{W} satisfies (2.2). Parameters $\pi \in (0, 1)$, and $\delta, \theta, \beta, \nu, r, \alpha$ are positive constants. The function $\mu \in L_+^\infty(0, \infty)$.*

State variables		Units	
S: Susceptible/non-lysogen bacteria density		CFU/g	
L: Lysogen bacteria density		CFU/g	
I: Lytic fated infected bacteria density		CFU/g	
P: Phages density		CFU/g	
Variable parameters	Range	Value	Source
A_{eff} : Antibiotics efficiency	0-1	{0.01, 0.15, 0.75, 0.95}	
P_{ind} : Induction probability	0-1	{0.01, 0.15, 0.75, 0.95}	
P_{ab} : Phage absorption probability	0-1	{0.01, 0.15, 0.75, 0.95}	
θ : Burst size of phage	5-400	{60, 200, 400}	[19, 38]
\mathcal{T}_S^0 : Bacteria reproductive number without any intervention	1 – 100	{10, 50, 100}	[14, 20]
π : Proportion of virulent cycle	0-0.9	{0.01, 0.15, 0.75, 0.95}	[2, 19]
τ : Latent period	10-100 min	{5, 10, 30}	[2, 19]
β : Phage absorption rate		calculated by (3.15)	
ν : Bacteria elimination rate		calculated by (3.15)	
α : Induction rate		calculated by (3.15)	
\mathcal{C} : Antibiotic steady-state		calculated by (3.15)	
Fixed parameters			
r_0 : Bacteria growth rate without antibiotic	0.1 – 3	1h ⁻¹	[14, 20]
\mathcal{C}_0 : Reduction rate of bacteria growth rate without antibiotic effects by 50%		4mg/L	Assumed
δ : Phages decay	0.1-3	1 h ⁻¹	[19]
$1/\kappa$: Bacteria carrying capacity with (2.3)	$10^4 - 10^{10}$	10^7 CFU/g	[14, 20]
$S(0)$: Initial size of sensitive bacteria		10^4 CFU/g	[20]
$L(0)$: Initial size of lysogen bacteria		10^4 CFU/g	[20]
$P(0)$: Phage initial density		10^7 CFU/g	[20].
Parameter to be analysed		Unit	
T_{op} : Time to achieve both non-lysogen and lysogen clearance			

CFU= colony-forming unit, *ie.*, the number of cells.

Table 1: Variables and parameters for Model (2.1).

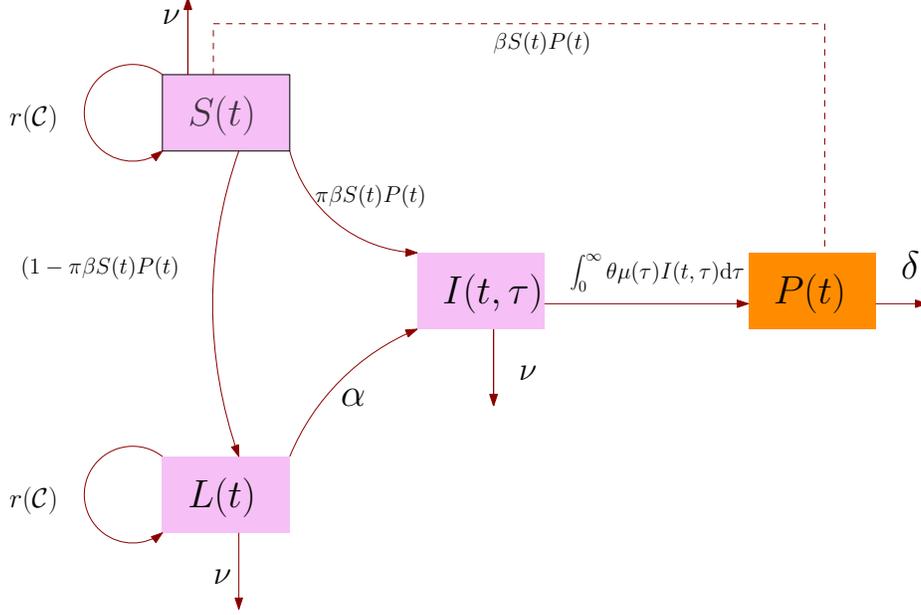


Figure 1: Phage-bacteria interaction with both horizontal and vertical transmissions during antibiotic phage combination therapy. The figure illustrates interactions, at any time t , between: susceptible or non-lysogen bacteria, $S(t)$, lysogen bacteria, $L(t)$, lytic-fated infected bacteria since time τ , $I(t, \tau)$, phages, $P(t)$.

Next, let us denote by

$$\mathbb{X} := \mathbb{R}^2 \times L^1(0, \infty, \mathbb{R}) \times \mathbb{R},$$

the Banach space endowed with its usual product norm $\|\cdot\|_{\mathbb{X}}$. Let

$$\mathbb{X}_+ := \mathbb{R}_+^2 \times L_+^1(0, \infty, \mathbb{R}) \times \mathbb{R}_+,$$

be the positive cone of \mathbb{X} . Let's rewrite (2.1) in the following form

$$\begin{cases} \dot{S}(t) = r(\mathcal{C})S(t)\mathcal{W}(S(t) + L(t)) - \beta S(t)P(t) - \nu S(t), \\ \dot{L}(t) = r(\mathcal{C})L(t)\mathcal{W}(S(t) + L(t)) + (1 - \pi)\beta S(t)P(t) - (\nu + \alpha)L(t), \\ 0 = -I(t, 0) + \pi\beta S(t)P(t) + \alpha L(t), \\ \partial_t I(t, \tau) = -\partial_\tau I(t, \tau) - (\nu + \mu(\tau))I(t, \tau), \\ \dot{P}(t) = \int_0^\infty \theta\mu(\tau)I(t, \tau)d\tau - \beta S(t)P(t) - \delta P(t). \end{cases} \quad (3.1)$$

120 Set $A : D(A) \subset \mathbb{X} \rightarrow \mathbb{X}$ the linear operator defined by $D(A) = \mathbb{R}^2 \times \{0\} \times W^{1,1}(0, \infty, \mathbb{R}) \times \mathbb{R}$ and

$$A(\varphi(t)) = \begin{pmatrix} -\nu S(t) \\ -(\nu + \alpha)L(t) \\ -I(t, 0) \\ -\partial_\tau I(t, \cdot) - (\nu + \mu(\tau))I(t, \cdot) \\ -\delta P(t) \end{pmatrix} \quad (3.2)$$

Set $G : \overline{D(A)} \rightarrow \mathbb{X}$ a non-linear application defined by

$$G(\varphi(t)) = \begin{pmatrix} r(\mathcal{C})S(t)\mathcal{W}(S(t) + L(t)) - \beta S(t)P(t) \\ r(\mathcal{C})L(t)\mathcal{W}(S(t) + L(t)) + (1 - \pi)\beta S(t)P(t) \\ \pi\beta S(t)P(t) + \alpha L(t) \\ 0_{L^1} \\ \int_0^\infty \theta\mu(\tau)I(t, \tau)d\tau - \beta S(t)P(t) \end{pmatrix}.$$

We also set $\mathcal{X}_0 = \overline{D(A)}$ and $\mathcal{X}_0^+ = \mathcal{X}_0 \cap \mathbb{X}_+$. The abstract Cauchy problem associated to (3.1) is the following

$$\begin{cases} \frac{d\varphi(t)}{dt} = A\varphi(t) + G(\varphi(t)) \\ \varphi(0) = \varphi_0 \in \mathcal{X}_0^+. \end{cases} \quad (3.3)$$

123 3.2 Global well-posedness, dissipativity and positivity

The abstract Cauchy problem (3.3) generates a unique globally defined and positive semiflow as follows.

Theorem 3.2 *Let Assumption 3.1 be satisfied. There exists a unique strongly continuous semiflow $\{\Psi(t) : \mathcal{X}_0^+ \rightarrow \mathcal{X}_0^+\}_{t \geq 0}$ such that, for all $\varphi_0 \in \mathcal{X}_0^+$, the map $\varphi \in \mathcal{C}([0, \infty), \mathcal{X}_0^+)$ defined by $\varphi = \Psi(\cdot)\varphi_0$ is a mild solution of (3.3) and satisfies for all $t \geq 0$*

$$\int_0^t \varphi(s)ds \in D(A), \quad \varphi(t) = \varphi_0 + A \int_0^t \varphi(s)ds + \int_0^t G(\varphi(s))ds.$$

126 *Moreover, setting $\Psi(t, \varphi_0) = (S(t), L(t), 0, I(t, \cdot), P(t))$, for all $\varphi_0 \in \mathcal{X}_0^+$. The semiflow $\{\Psi(t)\}_{t \geq 0}$ is such that*

(i) *The following integrated formulation holds:*

$$I(t, \tau) = \begin{cases} (\pi\beta S(t - \tau)P(t - \tau) + \alpha L(t - \tau)) \mathcal{D}(\tau), & \tau < t, \\ I(0, \tau - t) \frac{\mathcal{D}(\tau)}{\mathcal{D}(\tau - t)}, & \tau > t, \end{cases} \quad (3.4)$$

where $\mathcal{D}(\tau) = e^{-\int_0^\tau (\nu + \mu(\sigma))d\sigma}$, is the probability of a bacteria to remain alive τ -time after infection.

129 (ii) *The semiflow $\{\Psi(t)\}_{t \geq 0}$ is bounded dissipative and asymptotically smooth in the sens that*

Bounded dissipative: there exists a bounded set $\mathcal{B} \subset \mathcal{X}_0$ such that for any bounded set $\mathcal{C} \subset \mathcal{X}_0$, there exists $\xi = \xi(\mathcal{C}, \mathcal{B}) \geq 0$ such that $\Psi(t, \mathcal{C}) \subset \mathcal{B}$ for $t \geq \xi$.

132 *Asymptotically smooth: for any nonempty, closed, bounded set $\mathcal{C} \subset \mathcal{X}_0$, there exists a nonempty compact set $J = J(\mathcal{C})$ such that J attracts the set $\{\varphi \in \mathcal{C} : U(t, \varphi) \in \mathcal{C}, \forall t \geq 0\}$.*

Recall that a nonempty set $J \subset \mathcal{X}$ is said to attract a nonempty set $C \subset \mathcal{X}$ if $\delta_{\mathcal{X}}(U(t, C), J) \rightarrow 0$ as $t \rightarrow +\infty$, where $\delta_{\mathcal{X}}(C, J) = \sup_{u \in C} \inf_{v \in J} \|u - v\|_{\mathcal{X}}$ is a semi-distance on \mathcal{X} .

138 The existence and uniqueness of a semiflow associated with System (2.1) stated above is a quite standard result and can be specifically addressed using an integrated semigroup approach and Volterra integral formulation (eg., see [17, 24, 33, 36] and references therein). We refer to Section 5.1 for the detailed proof of Theorem 3.2.

3.3 Stationary states and asymptotic behavior

141 This section is devoted to the threshold dynamics of the System (2.1). We show that Model (2.1) has many trivial stationary states as opposed to a positive stationary state where all the variables are positive. Those stationary states lead to many stability regions that are precisely determined. Moreover, we show 144 that Model (2.1) exhibits a Hopf-bifurcation around the positive stationary state (the coexistence of all state variables) with the induction rate α as the bifurcation parameter.

Notice that the average number of susceptible (*ie.*, non-lysogen) and lysogen bacteria produced by a single bacterium during its entire lifespan are respectively quantified by

$$\mathcal{T}_S(\mathcal{C}) = \frac{r(\mathcal{C})}{\nu}, \quad \text{and} \quad \mathcal{T}_L(\mathcal{C}) = \frac{r(\mathcal{C})}{\nu + \alpha},$$

where we highlight the effect of the antibiotic concentration \mathcal{C} . Let us also introduce the quantity

$$\mathcal{K} = \int_0^\infty \theta \mu(\tau) \mathcal{D}(\tau) d\tau.$$

Note that \mathcal{K} is the total number of phages produced after the burst of infected bacteria.

147 We then have the following proposition

Proposition 3.3 *Let Assumption 3.1 be satisfied.*

150 *i) When $\mathcal{T}_S(\mathcal{C}) < 1$, the bacteria free steady state $\mathcal{O} = (0, 0, 0, 0)$ is the unique steady state of Model (2.1).*

ii) When $\mathcal{T}_S(\mathcal{C}) > 1$, Model (2.1) has a purely susceptible steady state $\mathcal{Q}_S = (S_0(\mathcal{C}), 0, 0, 0)$, with

$$S_0(\mathcal{C}) = \mathcal{W}^{-1} \left(\frac{1}{\mathcal{T}_S(\mathcal{C})} \right). \quad (3.5)$$

iii) When $\mathcal{T}_L(\mathcal{C}) > 1$, Model (2.1) has a purely lysogen steady state $\mathcal{Q}_L = (0, L_0(\mathcal{C}), I_0(\tau), P_0)$, with

$$L_0(\mathcal{C}) = \mathcal{W}^{-1} \left(\frac{1}{\mathcal{T}_L(\mathcal{C})} \right), \quad I_0(\tau) = \alpha \mathcal{D}(\tau) L_0(\mathcal{C}), \quad P_0 = \frac{\alpha \mathcal{K} L_0(\mathcal{C})}{\delta}. \quad (3.6)$$

When \mathcal{W} is a logistic function (2.3), we precisely have

$$S_0(\mathcal{C}) = \frac{1}{\kappa \mathcal{T}_S(\mathcal{C})} (\mathcal{T}_S(\mathcal{C}) - 1), \quad \text{and} \quad L_0(\mathcal{C}) = \frac{1}{\kappa \mathcal{T}_L(\mathcal{C})} (\mathcal{T}_L(\mathcal{C}) - 1).$$

In the case of a function of the form (2.4), we obtain

$$S_0(\mathcal{C}) = (\mathcal{T}_S(\mathcal{C}))^{1/\kappa} - 1, \quad \text{and} \quad L_0(\mathcal{C}) = (\mathcal{T}_L(\mathcal{C}))^{1/\kappa} - 1.$$

153 We refer to Section 5.2 for the proof of Proposition 3.3.

By the next-generation operator approach (see, [6, 18]) we compute the average number \mathcal{R}_0^S of phages produced by one phage in an entirely susceptible bacterial population $S_0(\mathcal{C})$, given by (3.5), as (see Section 5.3 for details)

$$\mathcal{R}_0^S(\mathcal{C}, \mathcal{P}) = \frac{\beta S_0(\mathcal{C})}{\beta S_0(\mathcal{C}) + \delta} \mathcal{K}.$$

156 Here, we also emphasize the influence of phage quantitative traits through the set of parameter $\mathcal{P} = (\beta, \alpha, \theta, \mu)$ introduced previously. In the above expression of \mathcal{R}_0^S , a total number of \mathcal{K} phages is produced by a single phage during its lifespan, and those phages are absorbed, by a susceptible bacteria population of size $S_0(\mathcal{C})$, with the probability $\beta S_0(\mathcal{C}) / (\beta S_0(\mathcal{C}) + \delta)$.

Similarly, the average number \mathcal{R}_0^L of new phages produced by an entirely lysogen bacterial population $L_0(\mathcal{C})$, given by (3.6), reads

$$\mathcal{R}_0^L(\mathcal{C}, \mathcal{P}) = \frac{\beta \mathcal{K} L_0(\mathcal{C})}{\delta}.$$

Next, we provide the stability results of above steady states.

159 **Theorem 3.4** *Let Assumption 3.1 be satisfied. Then,*

- i) *The steady state \mathcal{O} is globally asymptotically stable when $\mathcal{T}_S(\mathcal{C}) \leq 1$, an unstable elsewhere.*
- ii) *When $\mathcal{T}_S(\mathcal{C}) > 1$, the steady state \mathcal{Q}_S is locally asymptotically stable if and only if $\mathcal{R}_0^S(\mathcal{C}, \mathcal{P}) < 1$.*
- 162 iii) *When $\mathcal{T}_L(\mathcal{C}) > 1$, the steady state \mathcal{Q}_L is locally asymptotically stable if and only if $\mathcal{R}_0^L(\mathcal{C}, \mathcal{P}) > 1$.*

The prove of Proposition 3.4 is based on analyzing the spectral properties of the linearized semiflow at steady states of System (2.1). We refer to Section 5.5 fore more details.

165 We now focus on the existence of positive steady state of Model (2.1). The following result holds.

Proposition 3.5 *Let Assumption 3.1 be satisfied. Then, Model (2.1) admits a unique positive steady state, denote as $\mathcal{Q}^* = (S^*, L^*, I^*(\tau), P^*)$, if and only if*

$$\mathcal{T}_S(\mathcal{C}) > 1, \quad \mathcal{R}_0^S(\mathcal{C}, \mathcal{P}) > 1, \text{ and } \mathcal{R}_0^L(\mathcal{C}, \mathcal{P}) < 1. \quad (3.7)$$

Furthermore, we explicitly have

$$S^* = \frac{\left(\frac{1}{\mathcal{T}_L(\mathcal{C})} - \mathcal{W}^*\right) r(\mathcal{C})}{\beta \mathcal{K} \left(\pi r(\mathcal{C}) \left(\frac{1}{\mathcal{T}_L(\mathcal{C})} - \mathcal{W}^*\right) + \alpha(1 - \pi)\right)}, \quad L^* = \frac{\left(\mathcal{W}^* - \frac{1}{\mathcal{T}_S(\mathcal{C})}\right) (1 - \pi) r(\mathcal{C})}{\beta \mathcal{K} \left(\pi r(\mathcal{C}) \left(\frac{1}{\mathcal{T}_L(\mathcal{C})} - \mathcal{W}^*\right) + \alpha(1 - \pi)\right)},$$

and

$$I^*(\tau) = \frac{\left(\mathcal{W}^* - \frac{1}{\mathcal{T}_S(\mathcal{C})}\right) r(\mathcal{C})}{\beta \mathcal{K}} \mathcal{D}(\tau), \quad P^* = \frac{\left(\mathcal{W}^* - \frac{1}{\mathcal{T}_S(\mathcal{C})}\right) r(\mathcal{C})}{\beta},$$

where $\mathcal{W}^* := \mathcal{W}(S^* + L^*) \in \left(\frac{1}{\mathcal{T}_S(\mathcal{C})}, \frac{1}{\mathcal{T}_L(\mathcal{C})}\right)$ is the unique solution of the equation below :

$$\frac{\beta \mathcal{K} \left(\pi r(\mathcal{C}) \left(\frac{1}{\mathcal{T}_L(\mathcal{C})} - \mathcal{W}^*\right) + \alpha(1 - \pi)\right)}{\left(\left(\frac{1}{\mathcal{T}_L(\mathcal{C})} - \mathcal{W}^*\right) + (1 - \pi) \left(\mathcal{W}^* - \frac{1}{\mathcal{T}_S(\mathcal{C})}\right)\right) \left(\frac{1}{\mathcal{W}^{-1}(\mathcal{W}^*)}\right) \delta r(\mathcal{C})} = 1.$$

168 The proof of the above proposition is appended in Section 5.2.

We now turn to the local asymptotic behaviour of Model (2.1) around the positive steady state \mathcal{Q}^* . In this regard, we more precisely define the mortality rate μ of infected bacteria. Denote by $\varsigma > 0$, the time delay between phage adsorption and lysis. We assume that the rupture function $\mu(\cdot)$ takes the following form

$$\mu(\tau) = \begin{cases} 0 & \text{for } \varsigma < \tau, \\ \mu_0 & \text{for } \varsigma \geq \tau. \end{cases} \quad (3.8)$$

174 For any spectrum point λ (with $Re(\lambda) > -\min\{\nu, \delta\}$) of System (2.1), linearized around the positive steady state \mathcal{Q}^* , one has the following characteristic equation.

$$p(\lambda, \alpha) + q(\lambda, \alpha) e^{-\lambda \varsigma} = 0, \quad (3.9)$$

where $p(\lambda, \alpha)$ and $q(\lambda, \alpha)$ are of the form

$$p(\lambda, \alpha) = \lambda^4 + \sum_{k=0}^3 p_k \lambda^k, \quad q(\lambda, \alpha) = \sum_{k=0}^2 q_k \lambda^k.$$

Moreover, $p_k(\alpha) = p_k^0 + \mathcal{T}_L(\mathcal{C})p_k^1$, and $q_k(\alpha) = q_k^0 + \mathcal{T}_L(\mathcal{C})q_k^1$, with coefficients p_k^j, q_k^j in \mathbb{R} . Finally, any solution of the form $\lambda = i\omega$ ($\omega \in \mathbb{R}$) of the characteristic equation (3.9) around \mathcal{Q}^* is characterized by any pairing (ω, α) satisfying

$$\Gamma(\omega, \alpha) := \omega^8 + a_6\omega^6 + a_4\omega^4 + a_2\omega^2 + a_0 = 0, \quad (3.10)$$

and

$$\Gamma_1(\omega, \alpha) := \cos \omega\varsigma - \mathcal{Q}(\omega, \alpha) = 0, \quad (3.11)$$

where $\mathcal{Q} = \mathcal{Q}(\omega, \alpha)$ is a rational function defined by (5.21) and, a_k, s in Section 5.6 together with the coefficients depending (only) on p_k, s and q_k, s . We then have the following result :

Theorem 3.6 *Let Assumption 3.1 be satisfied. Assume that condition (3.7) for the existence of the positive steady state \mathcal{Q}^* holds. Let $(\omega_c > 0, \alpha_c > 0)$ such that condition (3.10)-(3.11) holds. Then, Model (2.1) undergoes a Hopf bifurcation, at the positive steady state \mathcal{Q}^* , for the critical value α_c , whenever we have*

$$\begin{aligned} \mathcal{M} := & (-3p_3\omega_c^2 + p_1) [p_0^1 - p_2^1\omega_c^2 + (q_0^1) \cos \omega_c\varsigma + (q_1^1\omega_c) \sin \omega_c\varsigma] \\ & + (4\omega_c^3 + 2p_2) [p_1^1\omega_0 + p_3^1\omega_c^3 + (q_1^1\omega_c) \cos \omega_c\varsigma - (q_0^1) \sin \omega_c\varsigma] \neq 0. \end{aligned}$$

Note that above condition ensures the transversality condition of the Hopf bifurcation theorem. We refer the interested reader to Section 5.6 for the proof of Theorem 3.6.

Remark 3.7 *In Theorem 3.6, the induction rate α is used as the bifurcation parameter. However, one may equivalently used the delay parameter ς as a bifurcation parameter. Indeed, let ω_0 a positive solution of (3.10). By the equality (3.11), we can find a sequence $(\varsigma_k)_{k=0,1,2,\dots}$ such that $\forall \alpha > 0$,*

$$\varsigma_k = \frac{1}{\omega_0} (\arccos(\mathcal{Q}(\omega_0, \alpha)) + 2k\pi), \quad k = 0, 1, 2, \dots, \quad (3.12)$$

and with the following transversality condition:

$$4\omega_0^3 + k \sum_{k=0}^3 a_k \omega_0^{k-1} \neq 0. \quad (3.13)$$

Thus, under condition (3.13), there exist ς_k defined in (3.12) such that Model (2.1) undergoes a Hopf bifurcation around the positive steady state \mathcal{Q}^* .

Figure 2 summarizes the qualitative analysis of Model (2.1) when $\mathcal{T}_S(\mathcal{C}) > 1$. For the configuration where $\mathcal{T}_S(\mathcal{C}) \leq 1$, \mathcal{O} is the unique steady state of Model (2.1) and is globally asymptotically stable.

3.4 Typical model simulation

For illustration purpose, we assume that the growth $r(\mathcal{C})$ is such that

$$r(\mathcal{C}) = r_0 \left(1 - \frac{\mathcal{C}}{\mathcal{C} + \mathcal{C}_0} \right),$$

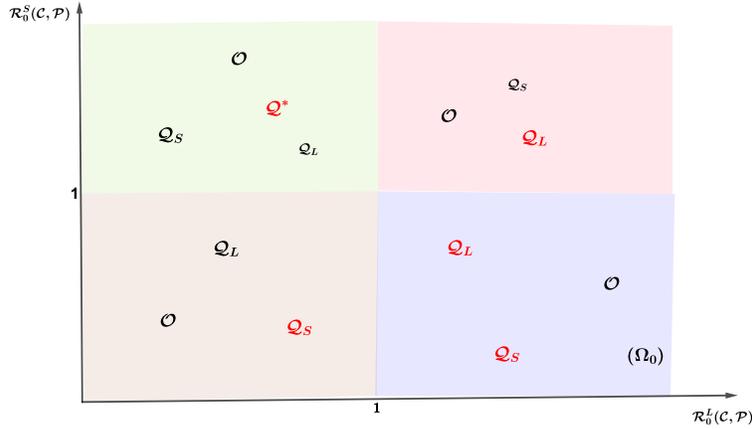


Figure 2: Qualitative analysis of Model (2.1) when $\mathcal{T}_S(\mathcal{C}) > 1$. In the $(\mathcal{R}_0^S, \mathcal{R}_0^L)$ -plane the positive orthant is divided into several regions. In each of them, plausible stationary states are illustrated, and stable steady states are in red. The region (Ω_0) is for the bistability of \mathcal{Q}_S and \mathcal{Q}_L .

192 where positive constants r_0 and \mathcal{C}_0 represent the bacteria growth rate without antibiotic effects and
the antibiotic concentration that reduces bacteria growth rate by 50%, respectively. Bacteria growth
regulation follows a logistic function as described in (2.3).

195 We now introduce the following quantitative parameters

$$\mathcal{T}_S^0 = \frac{r_0}{\nu}, \quad A_{\text{eff}} = \frac{\mathcal{C}}{\mathcal{C} + \mathcal{C}_0}, \quad P_{\text{ab}} = \frac{\beta S(\mathcal{C})}{\beta S(\mathcal{C}) + \delta}, \quad \text{and} \quad P_{\text{ind}} = \frac{\alpha}{\alpha + \nu}. \quad (3.14)$$

The parameters mentioned above facilitate model parameterization. Specifically, $\mathcal{T}_S^0 \in (1, \infty)$, $A_{\text{eff}} \in (0, 1)$, $P_{\text{ab}} \in (0, 1)$, and $P_{\text{ind}} \in (0, 1)$ respectively represent (i) the reproductive number of bacteria
198 without any intervention, (ii) the proportion of reduction in bacterial growth due to antibiotics, (iii) the
probability of phage absorption by susceptible bacteria of size $S(\mathcal{C})$ as introduced in Equation (3.5), and
(iv) the probability of prophage induction into the lysogenic cycle. With these parameters at our disposal,
201 which are of significant biological interest, (3.14) yields

$$\nu = \frac{r_0}{\mathcal{T}_S^0}, \quad \mathcal{C} = \frac{\mathcal{C}_0 A_{\text{eff}}}{1 - A_{\text{eff}}}, \quad \beta = \frac{\delta P_{\text{ab}}}{S(0)(1 - P_{\text{ab}})}, \quad \text{and} \quad \alpha = \frac{\nu P_{\text{ind}}}{1 - P_{\text{ind}}}. \quad (3.15)$$

For simulated scenarios, while all other model parameters are assumed constant with their reference
values given in Table 1, parameters \mathcal{T}_S^0 , A_{eff} , and $(\varsigma, \pi, \theta, P_{\text{ind}}, P_{\text{ab}})$ are assumed to be variables. \mathcal{T}_S^0
204 represents the initial bacterial growth capacity before any intervention, A_{eff} signifies the effectiveness of
antibiotics, and the parameter set $(\varsigma, \pi, \theta, P_{\text{ind}}, P_{\text{ab}})$ are related to the phage therapy.

As indicated by Proposition 3.3 and Theorem 3.4, Model (2.1) can exhibit local asymptotic stability
207 around the bacteria-free steady state \mathcal{O} , the purely susceptible steady state \mathcal{Q}_S , or the purely lysogenic
steady state \mathcal{Q}_L . However, here we focus on the numerical simulations illustrating the Hopf bifurcation
phenomenon around the positive steady state \mathcal{Q}^* (Theorem 3.6). Figure 3 illustrates a possible critical
210 pairing $(\omega_c > 0, \alpha_c > 0)$ given by the intersection of the level sets $\Gamma(\omega, \alpha) = 0$ and $\Gamma_1(\omega, \alpha) = 0$. We
then highlights the first bifurcation threshold value $\alpha_c \in (0.557, 0.563)$. By (3.14), such a threshold
value α_c of induction rate α is associated to a threshold value $P_{\text{ind}}^c \in (0.848, 0.849)$ of the probability of
213 prophage induction P_{ind} . Finally, Figures 4 illustrate a transcritical Hopf bifurcation, *ie.*, the appearance
of a limit cycle which is stable for values $P_{\text{ind}} = 0.849 > P_{\text{ind}}^c$ (Figure 4, B) and unstable for values
 $P_{\text{ind}} = 0.848 < P_{\text{ind}}^c$, giving rise to the stable positive steady state \mathcal{Q}^* (Figure 4, A).

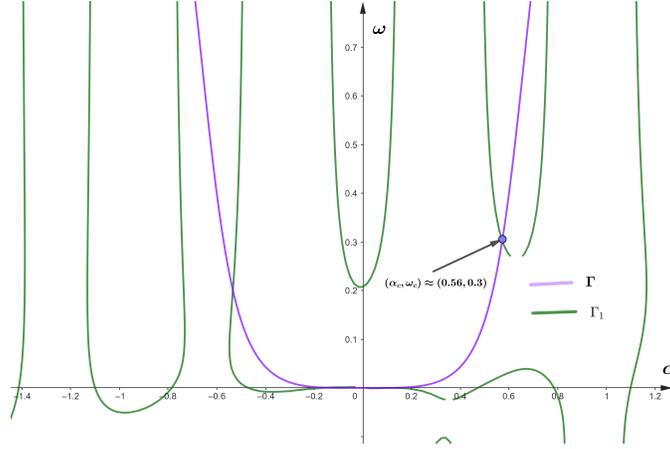


Figure 3: This figure illustrates a possible critical pairing ($\omega_c > 0, \alpha_c > 0$) given by the intersection of the level sets $\Gamma(\alpha, \omega) = 0$ and $\Gamma_1(\alpha, \omega) = 0$. It highlights the first bifurcation threshold value $\alpha_c \in (0.557, 0.563)$. Here, $\mathcal{T}_S^0 = 10$, $A_{\text{eff}} = 0.3$, $(\varsigma, \pi, \theta, P_{\text{ab}}) = (10, 0.1, 60, 6.6e-05)$, and other fixed parameters are given in Table 1.

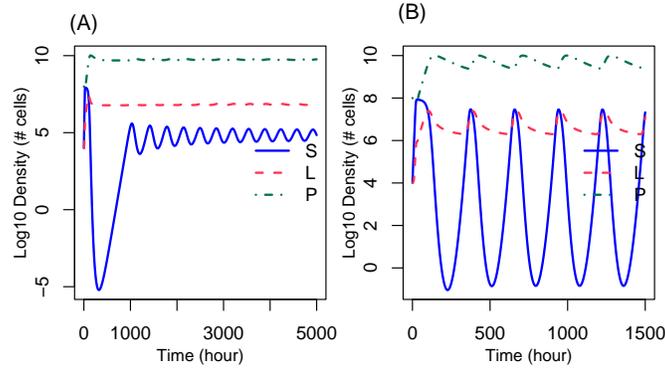


Figure 4: Illustration of the Hopf bifurcation around the positive steady state Q^* . (A) Asymptotic stability of the steady state Q^* for $P_{\text{ind}} = 0.848 < P_{\text{ind}}^c$. (B) The appearance of periodic solution for $P_{\text{ind}} = 0.849 > P_{\text{ind}}^c$. Here, $\mathcal{T}_S^0 = 10$, $A_{\text{eff}} = 0.3$, $(\varsigma, \pi, \theta, P_{\text{ab}}) = (10, 0.1, 60, 6.6e-05)$, and other fixed parameters are given in Table 1.

216 3.5 Global sensitivity analysis

When treating bacterial infections with a combination of antibiotics and phages, one may wish to know the situations in which using above interventions, as single or in combination, is effective in clearing bacteria load. The model proposed here allow to quantitatively assess key parameters that should be controlled to achieved effectiveness of interventions. Those parameters are \mathcal{T}_S^0 (the initial bacterial growth capacity before any intervention), A_{eff} (the effectiveness of antibiotics), and the set of parameters related to the phage therapy $(\varsigma, \pi, \theta, P_{\text{ind}}, P_{\text{ab}})$. We then perform a global sensitivity analysis of those parameters with respect to the quantitative parameter T_{op} defined as

$$T_{\text{op}} : \text{the minimum time from which, } \max(S(t), L(t)) < 10^{-20}, \text{ for all } t > T_{\text{op}}.$$

Note that, T_{op} represents the time for effective clearance of both susceptible (S) and lysogen (L) bacteria.

219 Global sensitivity analysis, as described by [29], quantifies the relative importance of parameters \mathcal{T}_S^0 , A_{eff} , and $(\varsigma, \pi, \theta, P_{\text{ind}}, P_{\text{ab}})$, by partitioning the variance of output variable T_{op} , into those resulting from

the main effects of the parameters and their higher-order interactions. The variation ranges for these parameters are provided in Table 1. Sensitivity indices were estimated by fitting an ANOVA (Analysis of Variance) linear model, which includes fourth-order interactions, to the simulation data. This ANOVA model fit well by explaining 98% of the variance. Overall, the sensitivity analysis results on the time for effective clearance of both susceptible and lysogen bacteria (T_{op}) indicates that ($P_{ind}, \mathcal{T}_S^0, P_{ab}, A_{eff}$) are the fourth main parameters in this order (Figure 5). Those parameters are followed by parameters (ς, θ) accounting for the burst of infected bacteria. Finally, the parameter π have marginal effect on the variability of T_{op} .

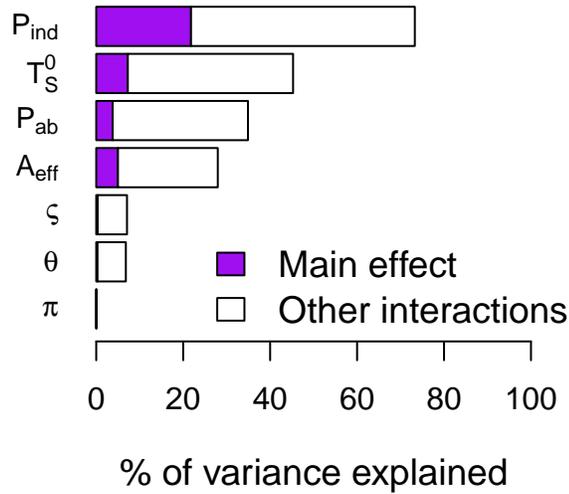


Figure 5: Sensitivity indices of the time for effective clearance of susceptible and lysogen bacteria, T_{op} . The colored portions of the bars represent the main indices, indicating the effect of each factor alone. In contrast, the full bars, which include both the colored and white parts, represent the total indices. The white sections of the bars illustrate the effect of each factor in interaction with all other factors.

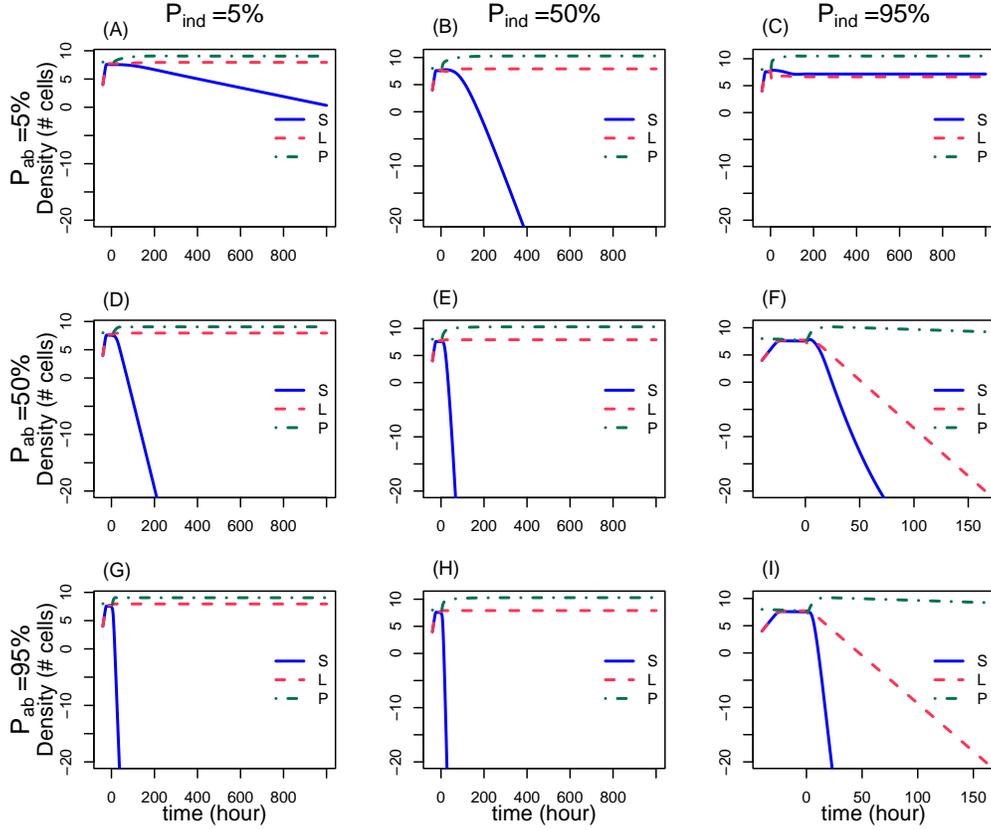


Figure 6: Model dynamics without any antibiotics effect. Phage therapy is introduced at the model positive steady state at time $t = 0$. Here we have, $\mathcal{T}_S^0 = 10$, $A_{\text{eff}} = 0$, $(\varsigma, \pi, \theta) = (5, 0.5, 60)$, and other fixed parameters are given in Table 1.

228 4 Conclusion and discussion

We address the role of antibiotic-phage combination treatment on within host bacteria growth and the influence of lysogeny on the success of phage therapy. Our approach is based on an age-structured mathematical model accounting for the time since infection (Model (2.1)). Such a modeling framework allows a refined description of the cell lysis phenomenon. We first handle the global well-posedness of the semiflow associated to System (2.1). We identify key threshold parameters for the asymptotic dynamics of the system and demonstrate that the model's qualitative behavior ranges from the extinction of all bacterial strains, to the persistence of a single strain, and the coexistence of all strains at a positive steady state (Figure 2). These threshold parameters include: the reproduction number of susceptible bacteria (\mathcal{T}_S), the reproduction number of lysogen bacteria (\mathcal{T}_L), and the reproduction number of phages (\mathcal{R}_0^S , and \mathcal{R}_0^L). Moreover, when the rupture phenomenon of infected bacteria is as in (3.8), System (2.1) undergoes a Hopf bifurcation around the positive steady state for some critical values of the induction rate (Figure 3 and 4).

For parametrization purpose, we introduce quantitative parameters $\mathcal{T}_S^0 \in (1, \infty)$, $A_{\text{eff}} \in (0, 1)$, $P_{\text{ab}} \in (0, 1)$, and $P_{\text{ind}} \in (0, 1)$ respectively representing (i) the reproductive number of bacteria without any intervention, (ii) the proportion of reduction in bacterial growth due to antibiotics, (iii) the probability of phage absorption by susceptible bacteria, and (iv) the probability of prophage induction. A global sensitivity analysis then highlights the main parameters impacting the time of effective bacterial clearance T_{op} (Figure 5). The sensitivity analysis indicates that $(P_{\text{ind}}, \mathcal{T}_S^0, P_{\text{ab}}, A_{\text{eff}})$ are the fourth main parameters.

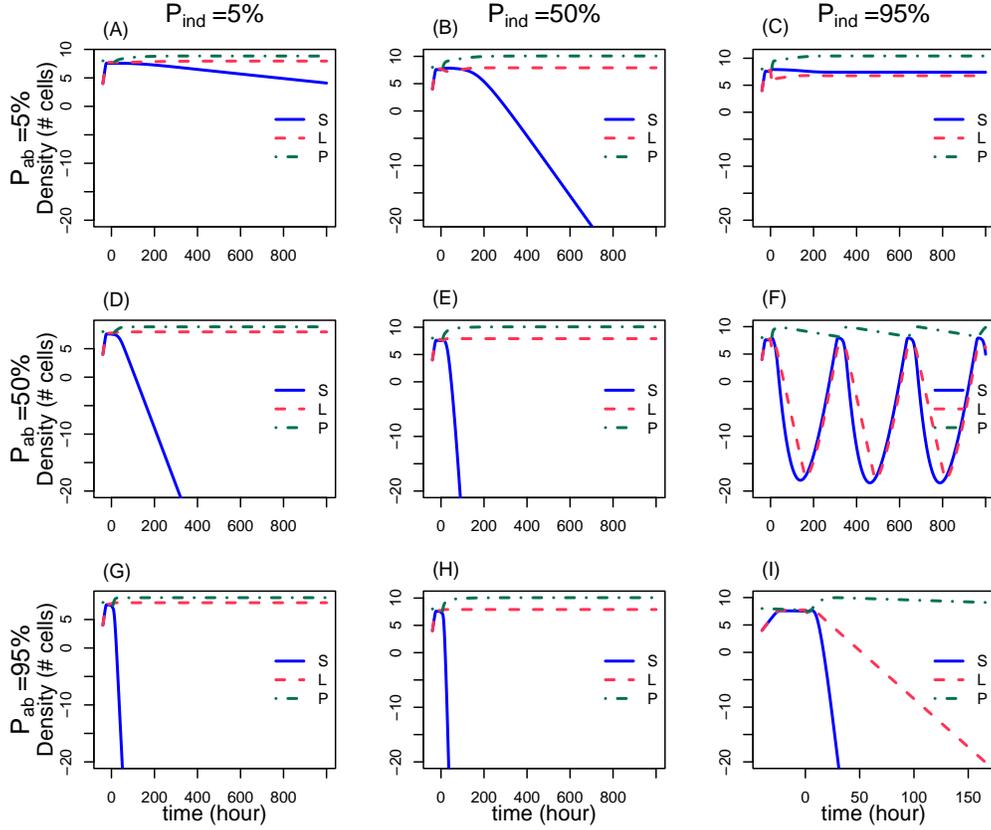


Figure 7: Same as in Figure 7 but with $\zeta = 10$.

The type of phages, whether purely lytic ($\pi = 1$) or temperate ($\pi < 1$), to be recommended for effective phage therapy can also be discussed. For instance, purely lytic phages are strongly recommended for phage therapy in [34]. However, the global sensitivity analysis shows that the parameter π (proportion of absorbed bacteria moving to the lytic-fated class) has a marginal effect on the variance of the time of effective bacterial clearance T_{op} (Figure 5). Therefore, the type of phage may not be crucial and allows for the use of temperate phages. This result aligns with findings in [3], where the authors recommend temperate phage-antibiotic synergy to eradicate bacteria through depletion of lysogen bacteria.

Optimizing quantitative traits such as the probability of phage absorption by susceptible bacteria (P_{ab}) and the probability of prophage induction into the lysogenic cycle (P_{ind}) can ensure effective bacterial clearance even without traditional antibiotic pressure. Consider a scenario where bacterial dynamics have reached a positive steady state before any treatment. At time $t = 0$, a phage therapy is implemented in the absence of any antibiotic effect (*ie.*, $A_{eff} = 0$). When the time delay between phage adsorption and lysis is relatively short ($\zeta = 5$), Figure 6 illustrates that combining an intermediate effect of P_{ab} with a strong effect of P_{ind} is sufficient to ensure effective bacterial clearance without any antibiotics (Figure 6, F,I). With a relatively long delay between phage adsorption and lysis, a strong effect of both parameters, P_{ab} and P_{ind} , is necessary to ensure effective bacterial clearance (Figure 7). Moreover, increasing the phage absorption probability (P_{ab}) significantly reduces the growth capability of susceptible bacteria, even when the induction probability (P_{ind}) is marginal (Figure 6, A,D,G). However, when P_{ab} is relatively low, moderate values of P_{ind} can significantly decrease the growth of susceptible bacteria (Figure 6, A, B, D, E). In contrast, if low P_{ab} values are combined with high P_{ind} values, there will be a slight reduction in lysogenic bacteria growth. This slight decrease, however (which is not enough to ensure effective lysogenic bacterial clearance), can promote the persistence of both susceptible and lysogenic bacteria due

to resource competition (Figure 6, C). The configuration remains unchanged when the time delay between phage adsorption and lysis increases from 5 (as shown in Figure 6) to 10 (as shown in Figure 7).

The above results emphasize the importance of selecting appropriate phages for therapeutic purposes. The selected viruses should have a good absorption capacity, which primarily contributes to the reduction of non-lysogen density (Figures 6A, D, G, and 7A, D, G). This aligns with findings from various studies in the field. For instance, in [2, 19], the results suggest that for effective phage therapy, phages with a broader host range are desired to infect and kill the widest range of pathogen strains or related species possible. Moreover, the time delay should be considered when developing phage protocols for controlling bacterial growth. Case F of Figures 6 and 7 clearly illustrates the importance of time delay. For short delays, the strong effect of P_{ind} and the intermediate effect of P_{ab} clear the infection, whereas a long time delay results in limit cycles around the positive steady state.

Lysogens may persist when the induction probability is small. Since lysogen bacteria are already infected by temperate phages (and thus immune to a second phage infection), ingestion of selected phages with good absorption capacity and short time delay may not be sufficient for treatment. In Figures 6 and 7, increasing P_{ab} from 5% to 95% may not be enough to control the infection, even when the time delay time is short. Achieving the non-persistence of lysogen bacteria is therefore a key target for treatment success. Fortunately, in such a configuration, the infection can be effectively under control by increasing the induction probability (Figures 5, 6F, I, and 7F, I). This aligns with results from [3], which suggest the use of inducers (such as acyl-homoserine lactones) to trigger the burst of lysogen bacteria.

The initial bacterial growth capability (\mathcal{T}_S^0) is essential when planning a phage therapy strategy. For instance, assume a configuration where the antibiotic effect is absent, and the phage quantitative traits are very strong with $P_{\text{ab}} = P_{\text{ind}} = 0.95\%$. In such a scenario, the outcome of the phage therapy will depend on the initial bacterial size (Figure 8). While the designed therapy is successful for some values of \mathcal{T}_S^0 (Figure 8A, B), it fails for higher values (Figure 8C). Therefore, when designing a phage therapy, either alone or in combination with antibiotics, it is important to take into account the initial bacterial growth capability (or size).

One limitation of the model proposed here is the absence of resistant bacteria to antibiotic and phage prey. Our next challenge is to investigate on the impact of mutations due to resistance during antibiotic-phage treatments. Some previous studies (*eg.* [16]) indicated that induction could be mainly associated with high temperature within the gut (intestine) environment. Consequently, induction is a random phenomenon that can be considered a stochastic process. Another potential limitation is the lack of the human immune system effect on the overall dynamics. A complete round-up will be to address the challenging modelling framework by combining antibiotics and phage-bacteria dynamics and the human immune system in a single within-host mathematical model. This is particularly important within the context of phage therapy as an alternative approach to reduce the emergence of antibiotic resistance. Furthermore, we assume that infected bacteria does not compete with non-lysogen and lysogen bacteria for resources. Such assumption is questionable particularly in a configuration where lytic and infected bacteria resist for an appreciable time before releasing phages.

5 Proof of Main results

5.1 Proof of Theorem 3.2

The existence and uniqueness of a semiflow associated with System (2) is a quite standard result (*eg.*, [24, 33]), as well as the Volterra formulation (*eg.*, [17, 36]).

For estimate (ii), let $\varphi_0 \in \mathcal{X}_{0+}$; then

$$\frac{d}{dt}(S(t) + L(t)) \leq r(\mathcal{C})(S(t) + L(t))\mathcal{W}(S(t) + L(t)) - \nu(S(t) + L(t)),$$

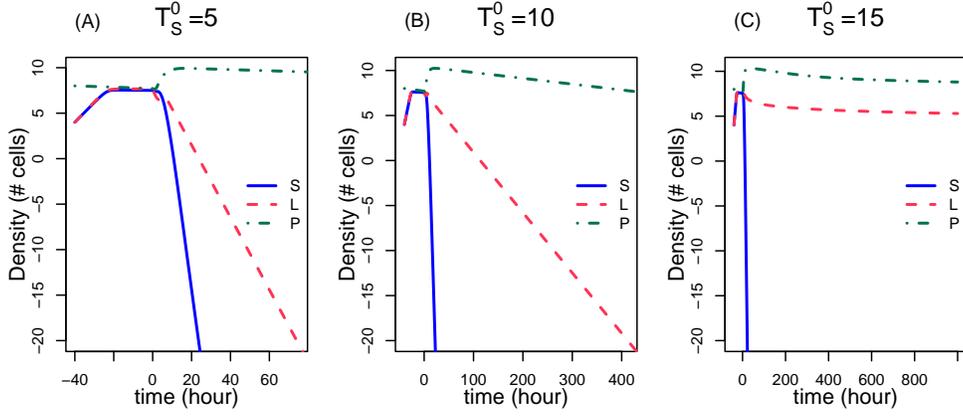


Figure 8: Model dynamics without any antibiotics effect and variable values of \mathcal{T}_S^0 . Phage therapy is introduced at the model positive steady state at time $t = 0$. Here we have, $A_{\text{eff}} = 0$, $(\varsigma, \pi, \theta) = (5, 0.5, 60)$, and other fixed parameters are given in Table 1.

Recalling that $\mathcal{W}(w) \in (0, 1]$ for all $w \in [0, w_0)$, it follows that

$$S(t) + L(t) \leq \begin{cases} \max\left(S(0) + L(0), \mathcal{W}^{-1}\left(\frac{\nu}{r(\mathcal{C})}\right)\right) & \text{if } \frac{\nu}{r(\mathcal{C})} \leq 1 \\ S(0) + L(0) & \text{if } \frac{\nu}{r(\mathcal{C})} > 1 \end{cases}$$

that is

$$S(t) + L(t) \leq \begin{cases} \max(S(0) + L(0), S_0(\mathcal{C})) & \text{if } \mathcal{T}_S(\mathcal{C}) \geq 1 \\ S(0) + L(0) & \text{if } \mathcal{T}_S(\mathcal{C}) < 1 \end{cases}$$

that is

$$S(t) + L(t) \leq \max(S(0) + L(0), \mathcal{W}^{-1}(\delta^\circ)),$$

312 with $\delta^\circ := \min\left(1, \frac{1}{\mathcal{T}_S(\mathcal{C})}\right)$. Next, by setting $B = S + L + \int I(\tau)d\tau$, it comes

$$\dot{B}(t) \leq \eta - \nu B(t),$$

with $\eta = \max(S(0) + L(0), \mathcal{W}^{-1}(\delta^\circ))$. From where

$$B(t) \leq \max\left\{\frac{\eta}{\nu}, B(0)\right\}. \quad (5.1)$$

Finally, we similarly find that

$$P(t) \leq \max\left\{\frac{\theta \|\mu\|_\infty}{\delta} \max\left(\frac{\eta}{\nu}, B(0)\right), P(0)\right\}. \quad (5.2)$$

315 Therefore, the bounded dissipativity of the semiflow $\{U(t) : \mathcal{X}_0^+ \rightarrow \mathcal{X}_0^+\}_{t \geq 0}$ is a consequence of estimates (5.1) and (5.2).

To prove the asymptotic smoothness, let C be a forward invariant bounded subset of \mathcal{X}_{0+} . By the results in [30], it is then sufficient to show that the semiflow U is asymptotically compact on the subset C . Let us introduce a sequence of solutions $(S^n, L^n, I^n, P^n)_n$ that is equibounded in \mathcal{X}_{0+} and a sequence $\{t_n\}_n$ such that $t_n \rightarrow +\infty$. Since the sequences S^n, L^n, P^n , are uniformly bounded in the Lipschitz norm, the Arzela-Ascoli theorem implies that, possibly along a subsequence, we can assume that the above

sequence is such that $S^n(t + t_n) \rightarrow \tilde{S}(t)$, $L^n(t + t_n) \rightarrow \tilde{L}(t)$, $I^n(t + t_n) \rightarrow \tilde{I}(t)$, and $P^n(t + t_n) \rightarrow \tilde{P}(t)$ locally uniformly for $t \in \mathbb{R}$. For the sequences $\{I^n\}_n$, Denote $\tilde{I}^n(t, \cdot) = I^n(t + t_n, \cdot)$. Then, the Volterra formulation (3.4) gives

$$\tilde{I}^n(t, \tau) = \begin{cases} (\pi\beta S^n(t - \tau + t_n)P^n(t - \tau + t_n) + \alpha L^n(t - \tau + t_n))\mathcal{D}(\tau), & \tau < t + t_n \\ I(0, \tau - t - t_n)\frac{\mathcal{D}(\tau)}{\mathcal{D}(\tau - t - t_n)}, & \tau > t + t_n \end{cases}$$

Since $(S^n(t - \tau + t_n)P^n(t - \tau + t_n) + L^n(t - \tau + t_n))\mathcal{D}(\tau)$ converges locally and uniformly towards the function $(\tilde{S}(t - \tau)\tilde{P}(t - \tau) + \tilde{L}(t - \tau))\mathcal{D}(\tau)$ as $t_n \rightarrow +\infty$, it comes

$$I^n(t_n, \cdot) = \tilde{I}^n(0, \cdot) \rightarrow (\tilde{S}(t - \cdot)\tilde{P}(t - \cdot) + \tilde{L}(t - \cdot))\mathcal{D}(\cdot) \text{ in } L^1(0, \infty, \mathbb{R}).$$

From where the asymptotic smoothness of the semiflow Ψ holds. Finally, the above estimates show that the semiflow Ψ is bounded dissipative, eventually bounded on bounded sets, and asymptotically smooth.

5.2 Existence of steady states

At any steady state $\mathcal{Q} = (S^*, L^*, I^*(\tau), P^*)$ one has:

$$r(\mathcal{C})S^*\mathcal{W}(S^* + L^*) - \beta S^*P^* - \nu S^* = 0, \quad (5.3)$$

$$r(\mathcal{C})L^*\mathcal{W}(S^* + L^*) + (1 - \pi)\beta S^*P^* - (\nu + \alpha)L^* = 0, \quad (5.4)$$

$$\frac{dI^*(\tau)}{d\tau} = -(\nu + \mu(\tau))I^*(\tau), \quad (5.5)$$

$$I^*(0) = \pi\beta S^*P^* + \alpha L^*,$$

$$\int_0^\infty \theta\mu(\tau)I^*(\tau)d\tau - \beta S^*P^* - \delta P^* = 0. \quad (5.6)$$

Solving (5.5) gives

$$I^*(\tau) = I^*(0)\mathcal{D}(\tau) = (\pi\beta S^*P^* + \alpha L^*)\mathcal{D}(\tau). \quad (5.7)$$

Putting (5.7) into (5.6) gives

$$P^* = \frac{\mathcal{K}(\pi\beta S^*P^* + \alpha L^*)}{\beta S^* + \delta}. \quad (5.8)$$

Set

$$\mathcal{W}^* = \mathcal{W}(S^* + L^*) \quad \text{then} \quad S^* + L^* = \mathcal{W}^{-1}(\mathcal{W}^*).$$

From (5.3), if $S^* = 0$, then (5.4), gives $L^* = 0$ or $L^* = L_0(\mathcal{C}) = \mathcal{W}^{-1}\left(\frac{1}{\mathcal{T}_L(\mathcal{C})}\right)$. From the properties of the function \mathcal{W} , the last equality holds only if $\mathcal{T}_L(\mathcal{C}) > 1$.

If $L^* = S^* = 0$, then (5.7) and (5.8) give $I^*(\tau) = P^* = 0$. Then the first steady state of (2.1) is $\mathcal{O} = (0, 0, 0, 0)$.

if $S^* = 0$, and $L^* = L_0(\mathcal{C})$, then (5.8) gives $P^* = P_0 = \alpha\mathcal{K}L_0(\mathcal{C})/\delta$, (5.7) gives $I^*(\tau) = I_0(\tau) = \alpha L_0(\mathcal{C})\mathcal{D}(\tau)$.

Assume now that $S^* > 0$, if $L^* = 0$, then $P^* = I^*(\tau) = 0$, and $S^* = \mathcal{W}\left(\frac{1}{\mathcal{T}_S(\mathcal{C})}\right)$. The latter holds only if $\mathcal{T}_S(\mathcal{C}) > 1$. For $L^* > 0$,

$$P^* = \frac{r(\mathcal{C})}{\beta} \left(\mathcal{W}^* - \frac{1}{\mathcal{T}_S(\mathcal{C})} \right), \quad \text{if } \mathcal{W}^* > \frac{1}{\mathcal{T}_S(\mathcal{C})}. \quad (5.9)$$

Putting (5.9) into (5.4) gives

$$(1 - \pi)S^* \left(\mathcal{W}^* - \frac{1}{\mathcal{T}_S(\mathcal{C})} \right) = \left(\frac{1}{\mathcal{T}_L(\mathcal{C})} - \mathcal{W}^* \right) L^*$$

330 under the condition

$$\frac{1}{\mathcal{T}_S(\mathcal{C})} < \mathcal{W}^* < \frac{1}{\mathcal{T}_L(\mathcal{C})}. \quad (5.10)$$

Looking for the existence of X^* such that (5.10) holds,

$$S^* = \frac{\left(\frac{1}{\mathcal{T}_L(\mathcal{C})} - \mathcal{W}^*\right) L^*}{(1 - \pi) \left(\mathcal{W}^* - \frac{1}{\mathcal{T}_S(\mathcal{C})}\right)}. \quad (5.11)$$

Putting (5.11) into (5.6) gives

$$L^* = \frac{\left(\mathcal{W}^* - \frac{1}{\mathcal{T}_S(\mathcal{C})}\right) (1 - \pi) r(\mathcal{C}) \delta}{\beta \pi \mathcal{K} r(\mathcal{C}) \left(\frac{1}{\mathcal{T}_L(\mathcal{C})} - \mathcal{W}^*\right) + \alpha \beta \mathcal{K} (1 - \pi)} \quad (5.12)$$

Putting (5.12) into (5.11), one has

$$S^* = \frac{\left(\frac{1}{\mathcal{T}_L(\mathcal{C})} - \mathcal{W}^*\right) r(\mathcal{C}) \delta}{\beta \pi \mathcal{K} r(\mathcal{C}) \left(\frac{1}{\mathcal{T}_L(\mathcal{C})} - \mathcal{W}^*\right) + \alpha \beta \mathcal{K} (1 - \pi)}$$

and

$$S^* + L^* = \frac{r(\mathcal{C}) \delta \left(\left(\frac{1}{\mathcal{T}_L(\mathcal{C})} - \mathcal{W}^*\right) + (1 - \pi) \left(\mathcal{W}^* - \frac{1}{\mathcal{T}_S(\mathcal{C})}\right) \right)}{\beta \pi \mathcal{K} r(\mathcal{C}) \left(\frac{1}{\mathcal{T}_L(\mathcal{C})} - \mathcal{W}^*\right) + \alpha \beta \mathcal{K} (1 - \pi)}.$$

Since, $S^* + L^* = \mathcal{W}^{-1}(\mathcal{W}^*)$ we have

$$\Phi(\mathcal{W}^*) = \Psi(\mathcal{W}^*).$$

Where

$$\Psi(\mathcal{W}^*) = \left(\frac{1}{\mathcal{W}^{-1}(\mathcal{W}^*)} \right) r(\mathcal{C}) \delta$$

and

$$\Phi(\mathcal{W}^*) = \frac{\beta \pi \mathcal{K} r(\mathcal{C}) \left(\frac{1}{\mathcal{T}_L(\mathcal{C})} - \mathcal{W}^*\right) + \alpha \beta \mathcal{K} (1 - \pi)}{\left(\frac{1}{\mathcal{T}_L(\mathcal{C})} - \mathcal{W}^*\right) + (1 - \pi) \left(\mathcal{W}^* - \frac{1}{\mathcal{T}_S(\mathcal{C})}\right)}.$$

Note that

$$\Psi'(\mathcal{W}^*) = - \left(\frac{(\mathcal{W}^{-1}(\mathcal{W}^*))'}{(\mathcal{W}^{-1}(\mathcal{W}^*))^2} \right) r(\mathcal{C}) \delta,$$

since \mathcal{W}^{-1} is decreasing, then Ψ is increasing. Moreover,

$$\Phi'(\mathcal{W}^*) = \frac{-\pi \mathcal{K} \beta (\nu + \alpha)}{\left(\left(\frac{1}{\mathcal{T}_L(\mathcal{C})} - \mathcal{W}^*\right) + (1 - \pi) \left(\mathcal{W}^* - \frac{1}{\mathcal{T}_S(\mathcal{C})}\right) \right)^2}.$$

Thus Φ is decreasing. Note that

$$\Phi(\mathcal{W}_0^*) = 0 \Leftrightarrow \mathcal{W}_0^* = \frac{1}{\mathcal{T}_L(\mathcal{C})} + \frac{\alpha \mathcal{K} (1 - \pi)}{r(\mathcal{C}) (\pi \mathcal{K})} > \frac{1}{\mathcal{T}_L(\mathcal{C})}.$$

333 Then there exists a unique positive steady state if and only if:

$$\Phi\left(\frac{1}{\mathcal{T}_L(\mathcal{C})}\right) < \Psi\left(\frac{1}{\mathcal{T}_L(\mathcal{C})}\right), \quad \text{and} \quad \Psi\left(\frac{1}{\mathcal{T}_S(\mathcal{C})}\right) < \Phi\left(\frac{1}{\mathcal{T}_S(\mathcal{C})}\right). \quad (5.13)$$

i) If $\mathcal{T}_L(\mathcal{C}) < 1$, we have

$$\Phi\left(\frac{1}{\mathcal{T}_L(\mathcal{C})}\right) = \beta\mathcal{K}r(\mathcal{C}), \quad \Psi\left(\frac{1}{\mathcal{T}_L(\mathcal{C})}\right) < 0.$$

and

$$\Psi\left(\frac{1}{\mathcal{T}_L(\mathcal{C})}\right) - \Phi\left(\frac{1}{\mathcal{T}_L(\mathcal{C})}\right) < 0$$

We also have

$$\Phi\left(\frac{1}{\mathcal{T}_S(\mathcal{C})}\right) = r(\mathcal{C})\beta(\mathcal{K} - 1), \quad \Psi\left(\frac{1}{\mathcal{T}_S(\mathcal{C})}\right) = \frac{r(\mathcal{C})\delta}{S_0(\mathcal{C})}$$

and

$$\Psi\left(\frac{1}{\mathcal{T}_S(\mathcal{C})}\right) - \Phi\left(\frac{1}{\mathcal{T}_S(\mathcal{C})}\right) = \frac{r(\mathcal{C})(\delta + \beta S_0(\mathcal{C})(1 - \mathcal{R}_0^S(\mathcal{C}, \mathcal{P})))}{S_0(\mathcal{C})}$$

Therefore when $\mathcal{T}_L(\mathcal{C}) < 1$, Condition (5.13) is equivalent to: $\mathcal{R}_0^S(\mathcal{C}, \mathcal{P}) > 1$.

ii) If $\mathcal{T}_L(\mathcal{C}) > 1$, then we have:

$$\Phi\left(\frac{1}{\mathcal{T}_L(\mathcal{C})}\right) = \beta\mathcal{K}r(\mathcal{C}), \quad \Psi\left(\frac{1}{\mathcal{T}_L(\mathcal{C})}\right) = \frac{r(\mathcal{C})\delta}{L_0(\mathcal{C})}.$$

and

$$\Psi\left(\frac{1}{\mathcal{T}_L(\mathcal{C})}\right) - \Phi\left(\frac{1}{\mathcal{T}_L(\mathcal{C})}\right) = \frac{r(\mathcal{C})\delta(1 - \mathcal{R}_0^L(\mathcal{C}, \mathcal{P}))}{L_0(\mathcal{C})}.$$

Similarly,

$$\Psi\left(\frac{1}{\mathcal{T}_S(\mathcal{C})}\right) - \Phi\left(\frac{1}{\mathcal{T}_S(\mathcal{C})}\right) = \frac{r(\mathcal{C})(\delta + \beta S_0(\mathcal{C})(1 - \mathcal{R}_0^S(\mathcal{C}, \mathcal{P})))}{S_0(\mathcal{C})}.$$

Therefore for $\mathcal{T}_L(\mathcal{C}) > 1$, Condition (5.13) is equivalent to:

$$\mathcal{R}_0^L(\mathcal{C}, \mathcal{P}) < 1, \quad \text{and} \quad \mathcal{R}_0^S(\mathcal{C}, \mathcal{P}) > 1.$$

This achieves the proof.

336 5.3 The basic reproduction number of phages

Let $N(t)$ be the number of newly produced phages at time t . We have

$$N(t) = \int_0^\infty \theta\mu(\tau)I(t, \tau)d\tau.$$

By the Volterra formulation (3.4) linearized at the purely susceptible steady state \mathcal{Q}_S , we find that

$$N(t) = \int_0^t \theta\mu(\tau)(\pi\beta S_0(\mathcal{C})P(t - \tau) + \alpha L(t - \tau))\mathcal{D}(\tau)d\tau + \int_t^\infty \theta\mu(\tau)I(0, \tau - t)\frac{\mathcal{D}(\tau)}{\mathcal{D}(\tau - t)}d\tau. \quad (5.14)$$

Moreover, we have

$$\dot{L}(t) = \left(\frac{r(\mathcal{C})}{\mathcal{T}_S(\mathcal{C})} - \nu - \alpha\right)L(t) + (1 - \pi)\beta S_0(\mathcal{C})P(t) = -\alpha L(t) + (1 - \pi)\beta S_0(\mathcal{C})P(t).$$

Therefore,

$$L(t) = \beta S_0(\mathcal{C})(1 - \pi) \int_0^t e^{-\alpha(t-s)}P(t - s)ds + L(0)e^{-\alpha t},$$

and consequently

$$N(t) = \int_0^t \pi\beta S_0(\mathcal{C})P(t-\tau)\mathcal{D}(\tau)d\tau + \alpha\theta(1-\pi)\beta S_0(\mathcal{C}) \int_0^t \int_0^\tau \mu(s)\mathcal{D}(s)e^{-\alpha(t-\tau-s)}dsP(t-\tau)d\tau + N_0(t), \quad (5.15)$$

339 where N_0 accounts for the initial condition.

Next, the P -equation of (2.1) linearized at \mathcal{Q}_S lead to

$$P(t) = \int_0^t e^{-(\beta S_0(\mathcal{C})+\delta)(t-s)}N(s)ds + e^{-(\beta S_0(\mathcal{C})+\delta)t}P(0),$$

Therefore, (5.14) and (5.15) respectively give

$$\begin{aligned} N(t) &= \pi\beta S_0(\mathcal{C}) \int_0^t \left(\int_0^{t-\tau} e^{-(\beta S_0(\mathcal{C})+\delta)(t-\tau-s)}N(s)ds \right) \mu(\tau)\mathcal{D}(\tau)d\tau \\ &+ \alpha\theta(1-\pi)\beta S_0(\mathcal{C}) \int_0^t \Lambda(\tau) \left(\int_0^{t-\tau} e^{-(\beta S_0(\mathcal{C})+\delta)(t-\tau-s)}N(s)ds \right) d\tau + N_0(t), \end{aligned}$$

with $\Lambda(\tau) = \int_0^\tau \mu(\sigma)\mathcal{D}(\sigma)e^{-\alpha(\tau-\sigma)}d\sigma$. That is

$$\begin{aligned} N(t) &= \pi\theta\beta S_0(\mathcal{C}) \int_0^t N(t-\tau) \left(\int_0^\tau e^{-(\beta S_0(\mathcal{C})+\delta)(\tau-s)}\mu(s)\mathcal{D}(s)ds \right) d\tau \\ &+ \alpha\theta(1-\pi)\beta S_0(\mathcal{C}) \int_0^t N(t-\tau) \left(\int_0^\tau e^{-(\beta S_0(\mathcal{C})+\delta)(\tau-s)}\Lambda(s)ds \right) d\tau + N_0(t), \end{aligned}$$

As $t \rightarrow \infty$, the basic reproduction number \mathcal{R}_0^S is calculated as

$$\mathcal{R}_0^S = \pi\theta\beta S_0(\mathcal{C}) \int_0^\infty \left(\int_0^\tau e^{-(\beta S_0(\mathcal{C})+\delta)(\tau-s)}\mu(s)\mathcal{D}(s)ds \right) d\tau + \alpha\theta(1-\pi)\beta S_0(\mathcal{C}) \int_0^\infty \left(\int_0^\tau e^{-(\beta S_0(\mathcal{C})+\delta)(\tau-s)}\Lambda(s)ds \right) d\tau,$$

Integrating above equality by parts, the basic reproduction number is

$$\mathcal{R}_0^S = \frac{\pi\beta S_0(\mathcal{C})\mathcal{K}}{(\beta S_0(\mathcal{C})+\delta)} + \frac{\alpha(1-\pi)\beta S_0(\mathcal{C})\mathcal{K}}{(\beta S_0(\mathcal{C})+\delta)\alpha} = \frac{\beta S_0(\mathcal{C})\mathcal{K}}{\beta S_0(\mathcal{C})+\delta}$$

5.4 Spectral properties of the linearized system

Let $\varphi^* = (S^*, L^*, 0, I^*(\tau), P^*) \in \mathcal{X}_0^+$ any steady state of problem (3.3). The derived linearized system at φ^* reads as:

$$\frac{d\varphi}{dt} = (A + G[\varphi^*])\varphi(t),$$

where A is the linear operator defined by (3.2), and $G[\varphi^*]$ is linear given by:

$$G[\varphi^*]\varphi(t) = \begin{pmatrix} r(\mathcal{C})[(\mathcal{W}^* + S^*\mathcal{W}^*)S(t) + S^*\mathcal{W}^*L(t)] - \beta P^*S(t) - \beta S^*P(t) \\ r(\mathcal{C})[L^*\mathcal{W}^*S(t) + (\mathcal{W}^* + L^*\mathcal{W}^*)L(t)] + (1-\pi)\beta S^*P(t) + (1-\pi)\beta P^*S(t) \\ \pi\beta S^*P(t) + \pi\beta P^*S(t) + \alpha L(t) \\ 0_{L^1(0,\infty,\mathbb{R})} \\ \int_0^\infty \theta\mu(\tau)I(t,\tau)d\tau - \beta S^*P(t) - \beta P^*S(t) \end{pmatrix},$$

with $\mathcal{W}^* = \mathcal{W}(S^* + L^*)$, and $\mathcal{W}^{\prime*} = \mathcal{W}'(S^* + L^*)$.

342 We now focus on the spectral properties of the linearized semiflow at any steady state. We have the following result :

Lemma 5.1 *Let us set $\Omega = \{\lambda \in \mathbb{C} : \operatorname{Re}(\lambda) > -\gamma\}$, with $\gamma = \min\{\nu, \delta\}$. Then, the spectrum $\sigma(A + G[\varphi^*]) \cap \Omega \neq \emptyset$ only consists of the point spectrum. Moreover, we have*

$$\sigma(A + G[\varphi^*]) \cap \Omega = \{\lambda \in \Gamma : \det \Delta(\lambda, \varphi^*) = 0\},$$

where the matrix $\Delta(\lambda, \varphi^*)$ is defined as

$$\Delta(\lambda, \varphi^*) = \begin{pmatrix} 1 - \frac{r(\mathcal{C})[\mathcal{W}^* + S^* \mathcal{W}^{*'}] - \beta P^*}{\lambda + \nu} & \frac{r(\mathcal{C})S^* \mathcal{W}^{*'}}{\lambda + \nu} & \frac{\beta S^*}{\lambda + \nu} \\ -\frac{r(\mathcal{C})L^* \mathcal{W}^{*'} + (1 - \pi)\beta P^*}{\lambda + \alpha + \nu} & 1 - \frac{r(\mathcal{C})[\mathcal{W}^* + L^* \mathcal{W}^{*'}]}{\lambda + \alpha + \nu} & -\frac{(1 - \pi)\beta S^*}{\lambda + \alpha + \nu} \\ \frac{\beta P^*(1 - \pi \mathcal{K}(\lambda))}{\lambda + \delta} & -\frac{\alpha \mathcal{K}(\lambda)}{\lambda + \delta} & 1 + \frac{\beta S^*(1 - \pi \mathcal{K}(\lambda))}{\lambda + \delta} \end{pmatrix}, \quad (5.16)$$

with $\mathcal{K}(\lambda) = \int_0^\infty \theta \mu(\tau) e^{-\int_0^\tau (\lambda + \nu + \mu(\sigma)) d\sigma} d\tau$.

Proof. We denote as $A_0 : D(A_0) \subset \mathcal{X}_0 \rightarrow \mathcal{X}_0$ the part of A in $\mathcal{X}_0 = D(A)$, ie.,

$$A_0 \varphi = A \varphi, \quad \forall \varphi \in D(A_0) = \{\varphi \in D(A) : A \varphi \in D(A)\}.$$

A_0 is the infinitesimal generator of a C_0 -semigroup on \mathcal{X}_0 denoted by $\{S_{A_0}(t)\}_{t \geq 0}$. Let $\varphi = (S, L, 0, I(\tau), P) \in \mathcal{X}_0$, then we have,

$$S_{A_0}(t) \varphi(\tau) = \begin{cases} (e^{-\nu t} S, e^{-(\nu + \alpha)t} L, 0, \mathcal{D}(\tau - t) I(\tau - t), e^{-\delta t} P), & \tau \geq t \\ (e^{-\nu t} S, e^{-(\nu + \alpha)t} L, 0, 0_{L^1(0, \infty, \mathbb{R})}, e^{-\delta t} P), & \tau < t. \end{cases}$$

Moreover, for $t \geq t_0$, we have

$$\|S_{A_0}(t - t_0) \varphi\|_{\mathcal{X}} \leq e^{-\gamma(t - t_0)} \|\varphi\|_{\mathcal{X}}, \quad t \geq t_0,$$

with $\gamma = \min(\nu, \delta)$. We then deduce that the growth rate $\omega_0(A_0)$ of the semigroup $\{S_{A_0}(t)\}_t$ generated by A_0 satisfies : $\omega_0(A_0) = \lim_{t \rightarrow \infty} \frac{\ln(\|S_{A_0}(t)\|_{\mathcal{L}(\mathcal{X})})}{t} \leq -\gamma$. The compactness of the operator $G[\varphi^*]$ gives that, the essential growth rate $\omega_{0, \text{ess}}(A + G[\varphi^*])$ of the C_0 -semigroup $\{S_{(A + G[\varphi^*])}(t)\}_{t \geq 0}$ generated by the part of $(A + G[\varphi^*])$ in \mathcal{X}_0 satisfies (eg., see [7]), $\omega_{0, \text{ess}}(A + G[\varphi^*]) \leq \omega_{0, \text{ess}}(A_0) < \omega_0(A_0) \leq -\gamma$. Thanks to [9, 35], the above inequality gives that $\Omega \cap \sigma(A + G[\varphi^*]) \neq \emptyset$, and it is only composed of point spectrum of $(A + G[\varphi^*])$.

We end the proof of Lemma 5.1 by computing the characteristic equation. Let $\lambda \in \rho(A + G[\varphi^*])$, where $\rho(A + G[\varphi^*])$ stands for the resolvent of $(A + G[\varphi^*])$. Let $\varphi = (S, L, 0, I, P) \in D(A)$ and $\tilde{\varphi} = (\tilde{S}, \tilde{L}, \tilde{w}, \tilde{I}, \tilde{P}) \in \mathcal{X}$. We have $(\lambda I - A - G[\varphi^*])\varphi = \tilde{\varphi}$, that is $(\lambda I - A)\varphi - G[\varphi^*]\varphi = \tilde{\varphi}$. Therefore,

$$\varphi - (\lambda I_d - A)^{-1} G[\varphi^*]\varphi = (\lambda I_d - A)^{-1} \tilde{\varphi}. \quad (5.17)$$

Since

$$(\lambda I_d - A)^{-1} \tilde{\varphi} = \left(\frac{\tilde{S}}{\lambda + \nu}, \frac{\tilde{L}}{\lambda + \nu + \alpha}, 0, \mathcal{D}_\lambda(\cdot) \tilde{w} + \int_0^\cdot \mathcal{D}_\lambda(\cdot - \eta) \tilde{I}(\eta) d\eta, \frac{\tilde{P}}{\lambda + \delta} \right),$$

it comes

$$(\lambda I_d - A)^{-1} G[\varphi^*]\varphi = \begin{pmatrix} (\lambda + \nu)^{-1} \left(r(\mathcal{C})[(\mathcal{W}^* + S^* \mathcal{W}^{*'})S + S^* \mathcal{W}^{*'}L] - \beta P^* S - \beta S^* P \right) \\ (\lambda + \nu + \alpha)^{-1} \left(r(\mathcal{C})[L^* \mathcal{W}^{*'}S + (\mathcal{W}^* + L^* \mathcal{W}^{*'})L] + (1 - \pi)\beta S^* P + (1 - \pi)\beta S P^* \right) \\ 0 \\ \mathcal{D}_\lambda(\cdot) (\pi \beta S^* P + \pi \beta P^* S + \alpha L) \\ (\lambda + \delta)^{-1} ((\pi \beta S^* P + \pi \beta P^* S + \alpha L) \mathcal{K}(\lambda) - \beta S^* P - \beta P^* S) \end{pmatrix},$$

where $\mathcal{D}_\lambda(\tau) = e^{-\int_0^\tau (\lambda + \nu + \mu(\sigma)) d\sigma}$ and $\mathcal{K}(\lambda) = \int_0^\infty \theta\mu(\tau) e^{-\int_0^\tau (\lambda + \nu + \mu(\sigma)) d\sigma} d\tau$.

Setting $(\lambda I_d - A)^{-1} \tilde{\varphi} = (\tilde{S}_\lambda, \tilde{L}_\lambda, 0, \tilde{I}_\lambda, \tilde{P}_\lambda)$, (5.17) leads to

$$I(\cdot) = (\pi\beta S^* P + \pi\beta P^* S + \alpha L) \mathcal{D}_\lambda(\cdot) + \tilde{I}_\lambda(\cdot).$$

Therefore, we can successfully isolate (S, L, P) , and so $(S, L, I(\cdot), P)$ if and only if

$$\det \Delta(\lambda, \varphi^*) \neq 0,$$

where $\Delta(\lambda, \varphi^*)$ is the matrix defined by (5.16). ■

357 5.5 Proof of Theorem 3.4

The proof of this result is based on the spectral properties of the linearized semiflow at any steady state of (2.1). The associated characteristic equation is provided by Lemma 5.1.

360 (i) From (5.16), and the fact that $\mathcal{W}(0) = 1$, we have:

$$\Delta(\lambda, \mathcal{O}) = \begin{pmatrix} \frac{\lambda + \nu - r(\mathcal{C})}{\lambda + \nu} & 0 & 0 \\ 0 & \frac{\lambda + \nu + \alpha - r(\mathcal{C})}{(\lambda + \nu + \alpha)} & 0 \\ 0 & -\frac{\alpha \mathcal{K}(\lambda)}{\lambda + \delta} & 1 \end{pmatrix},$$

such that, by Lemma 5.1,

$$\sigma(A + G[\mathcal{O}]) \cap \Omega = \{\nu(\mathcal{T}_S(\mathcal{C}) - 1), (\nu + \alpha)(\mathcal{T}_L(\mathcal{C}) - 1)\}.$$

Hence, \mathcal{O} is locally asymptotically stable if and only if $\max\{\mathcal{T}_S(\mathcal{C}), \mathcal{T}_L(\mathcal{C})\} = \mathcal{T}_S(\mathcal{C}) < 1$.

For the global stability of the steady state \mathcal{O} , we use a Lyapunov function approach. Let c the function such that

$$c : \tau \rightarrow \int_\tau^\infty \theta\mu(s) e^{-\int_s^\tau (\nu + \mu(\sigma)) d\sigma} ds.$$

Then, $c'(\tau) - (\nu + \mu(\tau))c(\tau) + \theta\mu(\tau) = 0$, and $\lim_{\tau \rightarrow \infty} c(\tau) = 0$. Let $t \in \mathbb{R} \mapsto \varphi(t) = (S(t), L(t), 0, I(t, \tau), P(t))$ be a complete orbit in the global attractor $\mathcal{B} \subset \mathcal{X}_0^+$ provided by Theorem 3.2. We introduce the following Lyapunov function,

$$\mathcal{L}[\varphi](t) = c(0)S(t) + c(0)L(t) + \int_0^\infty c(\tau)I(t, \tau) d\tau + P(t).$$

Differentiating \mathcal{L} along the trajectories gives :

$$\dot{\mathcal{L}}[\varphi](t) = c(0)\dot{S}(t) + c(0)\dot{L}(t) + \int_0^\infty c(\tau)\partial_t I(t, \tau) d\tau + \dot{P}(t)$$

Adding up the S - and L -equation of (2.1) gives,

$$\begin{aligned} \dot{\mathcal{L}}[\varphi](t) &= c(0)r(\mathcal{C})(S(t) + L(t))\mathcal{W}(S(t) + L(t)) - c(0)\pi\beta S(t)P(t) - \nu c(0)(S(t) + L(t)) - \alpha c(0)L(t) \\ &+ \int_0^\infty c(\tau)\partial_\tau I(t, \tau) - (\nu + \mu(\tau))I(t, \tau) d\tau + \int_0^\infty \theta\mu(\tau)I(t, \tau) d\tau - (\beta S(t) + \delta)P(t). \end{aligned}$$

Integrating the term $\int_0^\infty c(\tau)\partial_\tau I(t, \tau)d\tau$ by parts, it comes

$$\begin{aligned}\dot{\mathcal{L}}[\varphi](t) &= c(0) [r(\mathcal{C})\mathcal{W}(S(t) + L(t)) - \nu] (S(t) + L(t)) - c(0)\alpha L(t) - \pi c(0)\beta S(t)P(t) \\ &\quad - [c(\tau)I(t, \tau)]_0^\infty + \int_0^\infty [\partial_\tau c(\tau) - c(\tau)(\nu + \mu(\tau)) + \theta\mu(\tau)] I(t, \tau)d\tau - (\beta S(t) + \delta)P(t) \\ &= c(0)\nu [\mathcal{T}_S(\mathcal{C})\mathcal{W}(S(t) + L(t)) - 1] (S(t) + L(t)) - \beta S(t)P(t) - \delta P(t).\end{aligned}\quad (5.18)$$

If $\mathcal{T}_S(\mathcal{C}) < 1$, then,

$$\begin{aligned}\dot{\mathcal{L}}[\varphi](t) &\leq c(0)\nu [\mathcal{W}(S(t) + L(t)) - 1] (S(t) + L(t)) - \beta S(t)P(t) - \delta P(t) \\ &= c(0)\nu(S(t) + L(t)) [\mathcal{W}(S(t) + L(t)) - \mathcal{W}(0)] - \beta S(t)P(t) - \delta P(t)\end{aligned}$$

Since \mathcal{W} is a decreasing function, we have, $\dot{\mathcal{L}}[\varphi](t) \leq 0$, when $\mathcal{T}_S(\mathcal{C}) < 1$. Therefore, the map $t \rightarrow \mathcal{L}[\varphi](t)$ is decreasing along the entire solutions of the semiflow generated by (3.3) as soon as $\mathcal{T}_S(\mathcal{C}) < 1$. Furthermore, by (5.18), we have $\dot{\mathcal{L}}[\varphi](t) = 0$ if and only if $\varphi(t) = \mathcal{O}$. Then, the largest invariant set in $\{\varphi : \dot{\mathcal{L}}[\varphi] = 0\}$ is $\{\mathcal{O}\}$. From where, the global attractor \mathcal{B} is such that $\mathcal{B} = \{\mathcal{O}\}$, which leads to the global stability of \mathcal{O} in \mathcal{X}_+ when $\mathcal{T}_S(\mathcal{C}) < 1$.

(ii) From (5.16), we have

$$\Delta(\lambda, \mathcal{Q}_S) = \begin{pmatrix} \frac{\lambda - r(\mathcal{C})S_0(\mathcal{C})\mathcal{W}'(S_0(\mathcal{C}))}{\lambda + \nu} & \frac{r(\mathcal{C})S_0(\mathcal{C})\mathcal{W}'(S_0(\mathcal{C}))}{\lambda + \nu} & \frac{\beta S_0(\mathcal{C})}{\lambda + \nu} \\ 0 & \frac{\lambda + \alpha}{\lambda + \alpha + \nu} & -\frac{(1 - \pi)\beta S_0(\mathcal{C})}{\lambda + \alpha + \nu} \\ 0 & -\frac{\alpha\mathcal{K}(\lambda)}{\lambda + \delta} & 1 + \frac{\beta S_0(\mathcal{C})(1 - \pi\mathcal{K}(\lambda))}{\lambda + \delta} \end{pmatrix}.$$

Let $\lambda \in \sigma(A + G[\mathcal{Q}_S]) \cap \Omega$. By Lemma 5.1, we then have $\lambda = \lambda_0 := r(\mathcal{C})S_0(\mathcal{C})\mathcal{W}'(S_0(\mathcal{C}))$ or that λ is the solution of the following equation :

$$\mathcal{H}(\lambda) = 1, \quad (5.19)$$

with $\mathcal{H}(\lambda) = \frac{\alpha(1-\pi)\beta S_0(\mathcal{C})\mathcal{K}(\lambda)}{(\lambda+\alpha)(\lambda+\beta S_0(\mathcal{C})+\delta)} + \frac{\pi\beta S_0(\mathcal{C})\mathcal{K}(\lambda)}{(\lambda+\beta S_0(\mathcal{C})+\delta)}$. Since \mathcal{W} is a decreasing function, $\lambda_0 < 0$. Moreover, $\forall \lambda \in \mathbb{R}$, $\lim_{\lambda \rightarrow -\infty} \mathcal{H}(\lambda) = +\infty$, $\lim_{\lambda \rightarrow +\infty} \mathcal{H}(\lambda) = 0$, $\mathcal{H}'(\lambda) < 0$. Therefore, there exists a unique $\bar{\lambda} \in \mathbb{R}$ satisfying (5.19), and such that $\text{sign}(\bar{\lambda}) = \text{sign}(\mathcal{H}(0) - 1)$. Consequently, if $\mathcal{H}(0) = \mathcal{R}_0^S(\mathcal{C}, \mathcal{P}) > 1$, then the steady state \mathcal{Q}_S is unstable.

Next, we show that equations (5.19) has no complex solutions with non-negative real part whenever $\mathcal{R}_0^S(\mathcal{C}, \mathcal{P}) < 1$ (equivalently $\mathcal{H}(0) < 1$). By contradiction, assume that we can find $\lambda_0 \in \sigma(A + G[\mathcal{Q}_S]) \cap \Omega$ such that, $\Re(\lambda_0) \geq 0$. Set $\lambda_0 = x + iy$, with $x > 0, y \in \mathbb{R}$. Therefore,

$$\begin{aligned}1 = |\mathcal{H}(\lambda_0)| &\leq \frac{\alpha(1 - \pi)\beta S_0(\mathcal{C}) \int_0^\infty \theta\mu(\tau)\mathcal{D}(\tau)e^{-\tau x}d\tau}{(x + \alpha)(x + (\beta S_0(\mathcal{C}) + \delta))} + \frac{\pi\beta S_0(\mathcal{C}) \int_0^\infty \theta\mu(\tau)\mathcal{D}(\tau)e^{-\tau x}d\tau}{(x + \beta S_0(\mathcal{C}) + \delta)} \\ &= \mathcal{H}(x) \leq \mathcal{H}(0) = 1.\end{aligned}$$

A contradiction holds. Consequently, any solution of (5.19) has negative real part as soon as $\mathcal{R}_0^S(\mathcal{C}, \mathcal{P}) < 1$. Thus \mathcal{Q}_S is locally asymptotically stable if and only if $\mathcal{R}_0^S(\mathcal{C}, \mathcal{P}) < 1$.

(iii) From (5.16), one has

$$\Delta(\lambda, \mathcal{Q}_L) = \begin{pmatrix} \frac{\lambda - \alpha(1 - \mathcal{R}_0^L(\mathcal{C}, \mathcal{P}))}{\lambda + \nu}, & 0 & 0 \\ -\frac{r(\mathcal{C})L_0\mathcal{W}'(L_0) + (1 - \pi)\beta P_0}{\lambda + \nu + \alpha}, & \frac{\lambda - r(\mathcal{C})L_0\mathcal{W}'(L_0)}{\lambda + \nu + \alpha} & 0 \\ \frac{\beta\alpha\mathcal{K}L_0(1 - \pi\mathcal{K}(\lambda))}{\delta(\lambda + \delta)} & -\frac{\alpha\mathcal{K}(\lambda)}{\lambda + \delta} & 1 \end{pmatrix},$$

and Lemma 5.1 gives

$$\sigma(A + G[\mathcal{Q}_L]) \cap \Omega = \{r(\mathcal{C})L_0\mathcal{W}'(L_0); \alpha(1 - \mathcal{R}_0^L(\mathcal{C}, \mathcal{P}))\}.$$

375 Since \mathcal{W} is a decreasing function, we find that \mathcal{Q}_L is locally asymptotically stable if and only if $\mathcal{R}_0^L(\mathcal{C}, \mathcal{P}) > 1$.

5.6 Hopf bifurcation around the positive steady state

The proof of the bifurcation Theorem 3.6 is mainly based on the results in [22]. Let $\lambda \in \sigma(A + G[\mathcal{Q}^*]) \cap \Omega$. By Lemma 5.1, and recalling the rupture functions μ given by (3.8), then $\det \Delta(\lambda, \mathcal{Q}^*)$ takes the form:

$$\det \Delta(\lambda, \mathcal{Q}^*) = \frac{p(\lambda, \alpha) + q(\lambda, \alpha)e^{-\lambda\varsigma}}{(\lambda + \nu)(\lambda + \nu + \alpha)(\lambda + \delta)(\lambda + \nu + \mu_0)}$$

where

$$p(\lambda, \alpha) = \lambda^4 + p_3\lambda^3 + p_2\lambda^2 + p_1\lambda + p_0 \quad \text{and} \quad q(\lambda, \alpha) = q_2\lambda^2 + q_1\lambda + q_0.$$

378 with the coefficients $p_k, q_k, k = 1, 2, 3, 4$ in the form: $p_k = p_k^0 + p_k^1\mathcal{T}_L(\mathcal{C}), k = 1, 2, 3, 4$, with coefficients p_k^j, s in \mathbb{R} .

$$\det \Delta(\lambda, \mathcal{E}^*) = 0 \Leftrightarrow \mathcal{Z}(\lambda, \alpha) = p(\lambda, \alpha) + q(\lambda, \alpha)e^{-\lambda\varsigma} = 0 \quad (5.20)$$

Set $\lambda = i\omega, (\omega > 0)$, be a pure imaginary root of \mathcal{Z} , then (5.20) become:

$$p(i\omega, \alpha) + q(i\omega, \alpha)e^{-i\omega\varsigma} = 0,$$

implies that,

$$\cos \omega\varsigma = \frac{(-\omega^4 + \omega^2 p_2 - p_0)(q_0 - q_2\omega^2) + (\omega^3 p_3 - \omega p_1)q_1\omega}{(q_0 - q_2\omega^2)^2 + (q_1\omega)^2}. \quad (5.21)$$

381 Moreover, $|p(i\omega, \alpha)| = |q(i\omega, \alpha)|$; gives

$$\omega^8 + a_6\omega^6 + a_4\omega^4 + a_2\omega^2 + a_0 = 0 \quad (5.22)$$

with

$$a_6 = (p_3)^2 - 2p_2, a_4 = (p_2)^2 - (q_2)^2 + 2(p_0 - p_1 p_3), a_2 = (p_1)^2 - (q_1)^2 - 2(p_0 p_2 - q_0 q_2), .$$

and

$$a_0 = (p_0)^2 - (q_0)^2 = (p_0^0)^2 - (q_0^0)^2 + 2(p_0^0 p_0^1 - q_0^0 q_0^1)\mathcal{T}_L(\mathcal{C}) + ((p_0^1)^2 - (q_0^1)^2)(\mathcal{T}_L(\mathcal{C}))^2$$

Setting Δ the discriminant of the polynomial a_0 , some computations give:

$$\Delta = -4 [p_0^0 q_0^1 + q_0^0 p_0^1]^2$$

Assume

$$(p_0^0)^2 - (q_0^0)^2 < 0 \quad (5.23)$$

Since $\Delta < 0$, the polynomial $a_0 < 0$, for any positive value of $\mathcal{T}_L(\mathcal{C})$. Thus fixing a positive value \mathcal{T}_L^c (ie fixing a critical values α_c), under condition (5.23), (5.22) has positive solutions ω_c . Thus (5.22) has a positive root $z_c = \omega_c^2$. More over, for the fixed value of ς ,

$$\cos \omega_c \varsigma = \frac{(-(\omega_c)^4 + (\omega_c)^2 p_2 - p_0)(q_0 - q_2(\omega_c)^2) + ((\omega_c)^3 p_3 - (\omega_c) p_1)q_1(\omega_c)}{(q_0 - q_2(\omega_c)^2)^2 + (q_1(\omega_c))^2}$$

Transversality condition. Assume that (5.23) is satisfied, and let $\lambda(\alpha) = x(\alpha) + i\omega(\alpha)$ be the root of $\mathcal{Z}(\lambda, \alpha) = 0$ satisfying $x(\alpha_c) = 0$, $\omega(\alpha_c) = \omega_c$. Let's prove that $\Re\left(\frac{d\lambda(\alpha_c)}{d\alpha}\right) \neq 0$. Taking the derivative with respect to α on $\mathcal{Z}(\lambda, \alpha)$, we get

$$\begin{aligned} p_0^1 + p_1^1\lambda + p_2^1\lambda^2 + p_3^1\lambda^3 + (q_0^1 + q_1^1\lambda) e^{-\lambda\varsigma} &= (4\lambda^3 + 3p_3\lambda^2 + 2p_2\lambda + p_1) \frac{d\lambda}{d\alpha} \\ &+ (-\varsigma(q_0 + q_1\lambda + q_2\lambda^2 + q_3\lambda^3) + 2q_2\lambda + q_1) e^{-\lambda\varsigma} \frac{d\lambda}{d\alpha} \end{aligned}$$

then

$$\left(\frac{d\lambda(\alpha)}{d\alpha}\right)^{-1} = \frac{4\lambda^3 + 3p_3\lambda^2 + 2p_2\lambda + p_1 + (-\varsigma(q_0 + q_1\lambda + q_2\lambda^2 + q_3\lambda^3) + 2q_2\lambda + q_1) e^{-\lambda\varsigma}}{p_0^1 + p_1^1\lambda + p_2^1\lambda^2 + p_3^1\lambda^3 + (q_0^1 + q_1^1\lambda) e^{-\lambda\varsigma}}$$

Then substitute $\lambda = i\omega_c$ to obtain that

$$\Re\left\{\left(\frac{d\lambda(\alpha_c)}{d\alpha}\right)^{-1}\right\} = \frac{\mathcal{M}}{[p_0^1 - p_2^1\omega_c^2 + (q_0^1) \cos \omega_c\tau + (q_1^1\omega_c) \sin \omega_c\tau]^2 + [p_1^1\omega_c + p_3^1\omega_c^3 + (q_1^1\omega_c) \cos \omega_c\tau - (q_0^1) \sin \omega_c\tau]^2}$$

with

$$\begin{aligned} \mathcal{M} &= (-3p_3\omega_c^2 + p_1) [p_0^1 - p_2^1\omega_c^2 + (q_0^1) \cos \omega_c\tau + (q_1^1\omega_c) \sin \omega_c\tau] \\ &+ (4\omega_c^3 + 2p_2) [p_1^1\omega_c + p_3^1\omega_c^3 + (q_1^1\omega_c) \cos \omega_c\tau - (q_0^1) \sin \omega_c\tau] \end{aligned}$$

Moreover,

$$\text{sign}\left(\Re\left(\frac{d\lambda(\alpha_c)}{d\alpha}\right)^{-1}\right) = \text{sign}\left(\Re\left(\frac{d\lambda(\alpha_c)}{d\alpha}\right)\right).$$

The transversality condition holds if

$$\mathcal{M} \neq 0.$$

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387 Conflict of interest disclosure

The authors of this article declare that they have no financial conflict of interest with the content of this article.

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